Table of Pharmacogenomic Biomarkers in Drug Labeling
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Inclusion criteria: germline or somatic gene variants (polymorphisms, mutations), functional deficiencies with a genetic etiology, gene expression differences, chromosomal abnormalities; selected proteins that are used for treatment selection are also included;

Exclusion criteria: non-human genetic factors (e.g., viral or bacterial), biomarkers used for disease diagnostic purposes that are not used to determine dosing or treatment selection within the diagnosed disease, and biomarkers that are related to a drug other than the referenced drug (e.g., influences the effect of the referenced drug as a perpetrator of an interaction with another drug)

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>020977, 03/20/2017</td>
<td>Abacavir</td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING: HYPERSENSITIVITY REACTIONS, AND LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY</td>
</tr>
</tbody>
</table>

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with ZIAGEN® (abacavir). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele [see Warnings and Precautions (5.1)]. ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients [see Contraindications (4), Warnings and Precautions (5.1)]. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible [see Contraindications (4), Warnings and Precautions (5.1)]. Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms, including death, can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity [see Warnings and Precautions (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele Prior to Starting ZIAGEN
Screen for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN [see Boxed Warning, Warnings and Precautions (5.1)].

4 CONTRAINDICATIONS

ZIAGEN is contraindicated in patients:

• who have the HLA-B*5701 allele [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN® (abacavir). These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with ZIAGEN® (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment [see Adverse Reactions (6.1)]. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making. Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with ZIAGEN:

• All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment.

• ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.

• Before starting ZIAGEN, review medical history for prior exposure to any abacavir containing product. NEVER restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.

• To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).

• If a hypersensitivity reaction cannot be ruled out, do not restart ZIAGEN or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death, can occur within hours.

• A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

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<tr>
<td></td>
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<td></td>
<td>Reactions, Clinical Studies</td>
<td>VERZENIO® (abemaciclib) is indicated:</td>
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<td>• in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, nodepositive, early breast cancer at high risk of recurrence [see Clinical Studies (14.1)].</td>
</tr>
</tbody>
</table>

1.2 Advanced or Metastatic Breast Cancer
VERZENIO (abemaciclib) is indicated:
• in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
• in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
• as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

6 ADVERSE REACTIONS

14.1 Early Breast Cancer
monarchE, VERZENIO in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment
Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence The safety of VERZENIO was evaluated in monarchE, a study of 5591 adult patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine therapy (tamoxifen or an aromatase inhibitor) alone [see Clinical Studies (14.1)]. Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, plus tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of VERZENIO treatment was 24 months.

Advanced or Metastatic Breast Cancer
MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy
Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting
MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician’s choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 96% for the VERZENIO arm and 99% for the placebo arm. (…)

MONARCH 2: VERZENIO in Combination with Fulvestrant
Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy
The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2. (…)

MONARCH 1: VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer
Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting
Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unacceptable toxicity. Median duration of treatment was 4.5 months. (…)

14 CLINICAL STUDIES

14.1 Early Breast Cancer
VERZENIO in Combination with Standard Endocrine Therapy (monarchE)
Patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence monarchE (NCT03155997) was a randomized (1:1), open-label, two cohort, multicenter study in adult women and men with HR-positive, HER2-negative, node-positive, resected, early breast cancer with clinical and pathological features consistent with a high risk of disease recurrence. To be enrolled in cohort 1, patients had to have HR positive, HER2 negative early breast cancer with tumor involvement in at least 1 axillary lymph node (pALN) and either:
• > 24 pALN or
• 1-3 pALN and at least one of: – tumor grade 3 – tumor size ≥ 50 mm. Patients with available untreated breast tumor samples were tested retrospectively at central sites using the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay to establish if the Ki-67 score was ≥20%, specified in the protocol as “Ki-67 high”.

14.2 Advanced or Metastatic Breast Cancer
VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) (MONARCH 3)
Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting
MONARCH 3 was a randomized (2:1), double-blinded, placebo-controlled, multicenter study in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer. (…)

VERZENIO in Combination with Fulvestrant (MONARCH 2)

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|----------------------------------------|------|-----------------|--------------|-------------------|------------------|
| 208716, 03/03/2023                     | Abemaciclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Early Breast Cancer

**VERZENIO** (abemaciclib) is indicated:

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence [see Clinical Studies (14.1)].

1.2 Advanced or Metastatic Breast Cancer

**VERZENIO** (abemaciclib) is indicated:

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

6 ADVERSE REACTIONS

**Early Breast Cancer**

monarchE: VERZENIO in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment

- Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. The safety of VERZENIO was evaluated in monarchE, a study of 5991 adult patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine therapy (tamoxifen or an aromatase inhibitor) alone [see Clinical Studies (14.1)]. Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, plus tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of VERZENIO treatment was 24 months.

Advanced or Metastatic Breast Cancer

MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy

- Postmenopausal Women with HR-positive, HER2-negative, locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting.

MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician's choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm.

MONARCH 2: VERZENIO in Combination with Fulvestrant

- Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy.

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2. (…)

MONARCH 1: VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer

 Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting. Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months. (…)

14 CLINICAL STUDIES

14.1 Early Breast Cancer

VERZENIO in Combination with Standard Endocrine Therapy (monarchE)

- Patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence monarchE (NCT03155997) was a randomized (1:1), open-label, two cohort, multicenter study in 120 women and men with HR-positive, HER2-negative, node-positive, resected, early breast cancer with clinical and pathological features consistent with a high risk of disease recurrence. To be enrolled in cohort 1, patients had to have HR positive, HER2 negative early breast cancer with tumor involvement in at least 1 axillary lymph node (pALN) and either:

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<td><strong>Abemaciclib (3)</strong></td>
<td>Abemaciclib</td>
<td>Oncology</td>
<td>MK067</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<tr>
<td><strong>208716, 10/12/2021</strong></td>
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<td></td>
<td>14.1 Early Breast Cancer</td>
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<tr>
<td><strong>MONARCH 3</strong></td>
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<td>VERZENIO in Combination with an Aromatase Inhibitor (Aranzorozole or Letrozole) (MONARCH 3)</td>
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<tr>
<td><strong>208716, 10/12/2021</strong></td>
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<td></td>
<td>Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with prior systemic therapy in this disease setting</td>
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<tr>
<td><strong>213871, 01/14/2022</strong></td>
<td>Abrocitinib</td>
<td>Dermatology</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 USE IN SPECIFIC POPULATIONS</td>
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<td><strong>213871, 01/14/2022</strong></td>
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<td>8.8 CYP2C19 Poor Metabolizers</td>
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<tr>
<td><strong>VERZENIO in Combination with Fulvestrant (MONARCH 2)</strong></td>
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<td>Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy</td>
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<td><strong>MONARCH 2 (NCT02107703)</strong></td>
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<td>A randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting</td>
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<td><strong>MONARCH 1 (NCT02102490)</strong></td>
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<td></td>
<td>A single-arm open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting</td>
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<tr>
<td><strong>216340, 12/12/2022</strong></td>
<td>Adagrasib</td>
<td>Oncology</td>
<td>KRAS</td>
<td>Indications and Usage, Dosage and Administration,</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td><strong>VERZENIO in Combination with Fulvestrant (MONARCH 1)</strong></td>
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<td>Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting</td>
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<td></td>
<td>Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
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<td>2.1 Patient Selection</td>
<td>Select patients for treatment of locally advanced or metastatic NSCLC with KRAZATI based on the presence of KRAS G12C mutation in plasma or tumor specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests for the detection of a KRAS G12C mutation is available at: <a href="https://www.fda.gov/CompanionDiagnostics">https://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>6 ADVERSE REACTIONS</td>
<td>Non-Small Cell Lung Cancer</td>
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<td>6.1 Clinical Trials Experience</td>
<td>The safety of adagrasib was evaluated in patients with KRAS G12C-mutated, locally advanced or metastatic NSCLC in KRYSAL-1 [see Clinical Studies (14)]. Patients received adagrasib 600 mg orally twice daily (n = 116). Among patients who received adagrasib, 45% were exposed for 6 months or longer and 4% were exposed for greater than one year. (see Tables 3 and 4)</td>
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<tr>
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<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.3 Pharmacokinetics</td>
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<tr>
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<td></td>
<td>12.3 Pharmacokinetics</td>
<td>The pharmacokinetics of adagrasib were studied in healthy subjects and in patients with KRAS G12C-mutated NSCLC and are presented as mean (percent coefficient of variation) unless otherwise specified. Adagrasib AUC and Cmax increase dose proportionally over the dose range of 400 mg to 600 mg (0.67 to 1 times the approved recommended dose). Adagrasib steady-state was reached within 8 days following administration of the approved recommended dosage and accumulation was approximately 6-fold.</td>
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<td></td>
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<td>14 CLINICAL STUDIES</td>
<td>The efficacy of adagrasib was evaluated in KRYSAL-1 (NCT03786249), a multicenter, single-arm, open-label expansion cohort study. Eligible patients were required to have locally advanced or metastatic KRAS G12C-mutated NSCLC who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and at least one measurable lesion as defined by Response Evaluation criteria in Solid Tumors (RECIST v1.1). Identification of a KRAS G12C mutation was prospectively determined by local testing using tissue specimens. Patients received adagrasib 600 mg orally twice daily until unacceptable toxicity or disease progression. Tumor assessments were performed every 6 weeks. The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) as evaluated by blinded independent central review (BICR) according to RECIST v1.1. In the efficacy population, KRAS G12C mutation status was determined by prospective local testing using tumor tissue specimens. Of the 112 patients with KRAS G12C mutation, tissue samples from 88% (98/112) patients were tested retrospectively using the QIAGEN therascreen KRAS RGQ PCR Kit. While 89% (87/98) of patients were positive for KRAS G12C mutation, 11% (11/98) did not have a KRAS G12C mutation identified. In addition, plasma samples from 63% (71/112) patients were tested retrospectively using Agilent Resolution ctDx FIRST assay. While 66% (47/71) of patients were positive for KRAS G12C mutation, 34% (24/71) did not have a KRAS G12C mutation identified. (…)</td>
</tr>
</tbody>
</table>

125427, 05/03/2019 Ado-Trastuzumab Emtansine Oncology ERBB2 (HER2) Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies 1 INDICATIONS AND USAGE |
|                                        |      |                   |            | 1.1 Metastatic Breast Cancer (MBC) | KADCYLA®, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy. |
|                                        |      |                   |            | 1.2 Early Breast Cancer (EBC) | KADCYLA, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA [see Dosage and Administration (2.1)]. |
|                                        |      |                   |            | 2 DOSAGE AND ADMINISTRATION | 2.1 Patient Selection |
|                                        |      |                   |            | 2.1 Patient Selection | Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1), Clinical Studies (14)]. Assessment of HER2 protein overexpression and/or HER2 gene amplification should be performed using FDA-approved tests specific for breast cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics. Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. |
|                                        |      |                   |            | 6 ADVERSE REACTIONS | 6.1 Clinical Trials Experience |
|                                        |      |                   |            | 6.1 Clinical Trials Experience | Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the WARNINGS AND PRECAUTIONS reflect exposure to KADCYLA as a single agent at 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) in 1624 patients including 884 patients with HER2-positive metastatic breast cancer and 740 patients with HER2-positive early breast cancer (KATHERINE trial). |

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<th>Labeling Sections</th>
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<td>Neurology</td>
<td>APOE</td>
<td>Warnings and Precautions, Clinical Studies</td>
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<td>Afatinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse</td>
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**Metastatic Breast Cancer**

In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. The most common (≥25%) adverse reactions were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, constipation and epistaxis. The adverse reactions described in Table 3 were identified in patients with HER2-positive metastatic breast cancer treated in the EMILIA trial [see Clinical Studies (14.1)]. Patients were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.5 months for patients treated with lapatinib and capecitabine, respectively. (…)

**Early Breast Cancer**

KADCYLA has been evaluated as a single-agent in 740 patients with HER2-positive early breast cancer. The adverse reactions described in Table 5 were identified in patients with HER2-positive early breast cancer treated in the KATHERINE trial [see Clinical Studies (14.2)]. Patients were randomized to receive KADCYLA or trastuzumab. The median duration of study treatment was 12 months for patients in the KADCYLA-treated group and 10 months for patients treated with trastuzumab. (…)

---

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

**Cardiac Electrophysiology**

The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open-label, single-arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

**12.3 Pharmacokinetics**

**Effect of Hepatic Impairment**

The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment. (…)

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**14 CLINICAL STUDIES**

**14.1 Metastatic Breast Cancer**

The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial (EMILIA) (NCT00829166) of 991 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only prior adjuvant therapy were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥2.0 determined at a central laboratory. (…)

**14.2 Early Breast Cancer**

KATHERINE (NCT01772472) was a randomized, multicenter, open-label trial of 1496 patients with HER2-positive, early breast cancer. Patients were required to have had no adjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥2.0 determined at a central laboratory using Ventana’s PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent(s), and pathological nodal status evaluation after preoperative therapy.

KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. (…)

The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 84% of these patients received pertuzumab. (…)

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**5 WARNINGS AND PRECAUTIONS**

**5.1 Amyloid Related Imaging Abnormalities**

ARIA-E was observed in 35% of patients treated with ADUHELM 10 mg/kg, compared to 3% of patients on placebo. The incidence of ARIA-E was higher in ApoE ε4 non-carriers (42% and 20%, respectively). (…)

**5.2 Cardiac Impairment**

Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. (…)

**5.3 Human Immunodeficiency Virus (HIV)**

In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

**5.4 Hepatic Impairment**

The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment. (…)

**5.5 Renal Impairment**

In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

**Cardiac Electrophysiology**

The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open-label, single-arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

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**14 CLINICAL STUDIES**

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**2 INDICATIONS AND USAGE**

**1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer**

GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see Clinical Pharmacology (12.1) and Clinical Studies (14.1)].
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<th>Biomarker</th>
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<td>Oncology</td>
<td>ALK</td>
<td>Reactions, Clinical Studies</td>
<td>Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations (see Clinical Studies (14.1)).</td>
</tr>
</tbody>
</table>

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC

- Select patients with metastatic NSCLC harboring non-resistant EGFR mutations (Stage IV and Stage IIIb with pleural and/or pericardial effusion) for the treatment of NSCLC with ALECENSA based on the presence of nonresistant EGFR mutations in tumor specimens (see Indications and Usage (1.1) and Clinical Studies (14.1)). Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

- GILOTRIF is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic NSCLC, in LUX-Lung 8, and in LUX-Lung 3, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy (…).

#### 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

The data below reflect the exposure of 229 patients with EGFR mutation-positive, metastatic NSCLC, and in LUX-Lung 8, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy (…).

- **14 CLINICAL STUDIES**

#### 14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer

The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition) non-small cell lung cancer (NSCLC), as randomized, were established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trialassy (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic therascreen® EGFR RQG PCR Kit, which is FDA-approved for the detection of patients for GILOTRIF treatment.

Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian, and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

- Pre-specified exploratory subgroup analyses were conducted according to the stratification factor of EGFR mutation category. See Figure 2 and text below Figure 2.

- **Overall Response Rate in Other EGFR Mutations**

The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (7681, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions was evaluated in a pooled analysis of such patients enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148]. LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT0121393]).

- **LUX-Lung 2** was a single arm, multicenter study of afatinib 40 mg or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue.

- **LUX-Lung 6** was a randomized, multicenter study comparing treatment with afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m² plus pemetrexed 500 mg/m² every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit.

- **LUX-Lung 3** was a randomized, multicenter study comparing treatment with afatinib 40 mg to intravenous gemcitabine 1000 mg/m² on day 1 and day 8 plus cisplatin 75 mg/m² on day 1 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit.

- Among the 32 patients with a confirmed non-resistant EGFR mutation, the median age was 60.5 years (range 32-79), 66% were female, 97% were Asian, 3% were other races, 38% had an EGFR PS of 0, 63% had an EGCO PS of 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIIb disease, and 88% had received no prior systemic therapy for advanced or metastatic disease. The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.

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Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 12/2023

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<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<td>12/16/2020, 020298</td>
<td>Alectinib</td>
<td>Oncology</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
<td>WARNINGS: DISCONTINUE ALOPRIM AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE A HYPERSENSITIVITY REACTION. Discontinue ALOPRIM immediately if severe cutaneous reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) or systemic symptoms (e.g., severe rash, fever) develop.</td>
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<td>12/16/2020, 020298</td>
<td>Allopurinol</td>
<td>Oncology</td>
<td>2.2 Immune-Mediated Reactions</td>
<td>Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrolyzing skin lesions [see Adverse Reactions (6.3)]. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alglucosidase alfa. These reactions occurred within 3 years after initiation of alglucosidase alfa infusions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with pyrexia and elevated erythrocyte sedimentation rate. Nephrotic syndrome secondary to membranous glomerulonephritis was observed in some Pompe disease patients treated with alglucosidase alfa who had persistently positive anti-rhGAA IgG antibody titers. In these patients, renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. Therefore, patients receiving alglucosidase alfa should undergo periodic urinalysis [see Adverse Reactions (6.3)].</td>
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<td>Alpelisib (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.</td>
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<td>Alpelisib (2)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.</td>
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<td>212526, 05/04/2022</td>
<td>Alpelisib (3)</td>
<td>Oncology</td>
<td>PIK3CA</td>
<td>Indication and Usage, Dosage and Administration,</td>
<td>PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.</td>
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<td>Neurology</td>
<td>NAT2</td>
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</table>

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**
Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests for the detection of PIK3CA mutations in breast cancer is available at: [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

**6 ADVERSE REACTIONS**

**6.1 Clinical Trial Experience**
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**14 CLINICAL STUDIES**
SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s). Overall, 60% of enrolled patients had tumors with one or more PIK3CA mutations in tissue, 50% had liver/lung metastases, and 6% had previously been treated with a CDK4/6 inhibitor.

There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. Of the 341 patients in the cohort with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the FDA-approved therascreen® PIK3CA RQq PCR Kit. Out of the 336 patients with PIK3CA mutations confirmed in tumor tissue, 19 patients had no plasma specimen available for testing with the FDA-approved therascreen® PIK3CA RQq PCR Kit. Of the remaining 317 patients with PIK3CA mutations confirmed in tumor tissue, 177 patients (56%) had PIK3CA mutations identified in plasma specimen, and 140 patients (44%) did not have PIK3CA mutations identified in plasma specimen. (…) Patient demographics for those with PIK3CA-mutated tumors were generally representative of the broader study population. The median duration of exposure to PIQRAY plus fulvestrant was 8.2 months with 59% of patients exposed for > 6 months. (…) The major efficacy outcome was investigator-assessed progression-free survival (PFS) in the cohort with a PIK3CA mutation per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall response rate (ORR) and overall survival (OS) in the cohort with a PIK3CA mutation.

Efficacy results for the cohort with a PIK3CA mutation in tumor tissue are presented in Table 8 and Figure 1. PFS results for the cohort with a PIK3CA mutation by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. Consistent results were seen in patients with tissue or plasma PIK3CA mutations. At the time of final PFS analysis, 27% (92/341) of patients had died, and overall survival follow-up was immature. No PFS benefit was observed in patients whose tumors did not have a PIK3CA tissue mutation (HR = 0.85; 95% CI: 0.58, 1.25). (See Table 8 and Figure 1)

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| 208078, 11/28/2018                    | Amifampridine Phosphate | Neurology  | NAT2 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION  
2.4 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers  
The recommended starting dosage of FIRDAPSE in known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily, taken orally in 3 divided doses [see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3, 12.5)]. |
| 207356, 02/10/2023                    | Amikacin | Infectious Diseases | MT-RNR1 | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.6 Ototoxicity  
**Oxotremorine with use of ARIKAYCE**  
Oxotremorine has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported with a higher frequency in patients treated with ARIKAYCE plus a background regimen (17%) compared to patients treated with background regimen alone (9.6%). This was primarily driven by tinnitus (8.1% in ARIKAYCE plus background regimen vs. 0.9% in the background regimen alone arm) and dizziness (6.3% in ARIKAYCE plus background regimen vs. 2.7% in the background regimen alone arm) [see Adverse Reactions (6.1)].  
Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage the patient as medically appropriate, including potentially discontinuing ARIKAYCE.  
Risk of Ototoxicity Due to Mitochondrial DNA Variants  
Cases of ototoxicity with aminoglycosides have been observed in patients with certain variants in the mitochondrially encoded 12S rRNA gene (MT-RNR1), particularly the m.1555A>G variant. Ototoxicity occurred in some patients even when their aminoglycoside serum levels were within the recommended range. Mitochondrial DNA variants are present in less than 1% of the general US population, and the proportion of the variant carriers who may develop ototoxicity as well as the severity of ototoxicity is unknown. In cases of known maternal history of ototoxicity due to aminoglycoside use or a known mitochondrial DNA variant in the patient, consider alternative treatments other than aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the severity of infection and lack of safe and effective alternative therapies. |
| 085971, 07/17/2014                    | Amitriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS  
Drugs Metabolized by P450 2D6  
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).  
In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. (…)

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<td>Usage, Dosage and</td>
<td>RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)], whose disease has progressed on or after platinum-based chemotherapy. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.</td>
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<td>Administration, Adverse Reactions, Clinical Studies</td>
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<tr>
<td>07/17/2014</td>
<td>072691</td>
<td>Amoxapine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>Drugs Interactions</td>
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<td>Drugs Metabolized by P450 2D6</td>
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<td>The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).</td>
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<td>In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy.</td>
</tr>
<tr>
<td>09/15/2017</td>
<td>204325</td>
<td>Amphetamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<tr>
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<td>12.2 Pharmacokinetics</td>
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<td>Elimination</td>
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<td>Metabolism and Excretion</td>
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<td>Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4 hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylaceton, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.</td>
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<tr>
<td>12/18/2020</td>
<td>103950</td>
<td>Anakinra</td>
<td>Rheumatology</td>
<td>NLRP3</td>
<td>Indications and</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Usage, Dosage</td>
<td>ANKIRIN is indicated for the treatment of active inflammatory joint disease.</td>
</tr>
</tbody>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
|                                   |                   |            |                   | KINERET is indicated for the treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID).
|                                   |                   |            |                   | 2 DOSAGE AND ADMINISTRATION |
|                                   |                   |            |                   | 2.2 Cryopyrin-Associated Periodic Syndromes (CAPS) |
|                                   |                   |            |                   | The recommended starting dose of KINERET is 1-2 mg/kg for NOMID patients. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. Adjust doses in 0.5 to 1 mg/kg increments. Once daily administration is generally recommended, but the dose may be split into twice daily administrations. Each syringe is intended for a single use. A new syringe must be used for each dose. Any unused portion after each dose should be discarded. |
|                                   |                   |            |                   | 5 WARNINGS AND PRECAUTIONS |
|                                   |                   |            |                   | 5.1 Serious Infections |
|                                   |                   |            |                   | KINERET has been associated with an increased incidence of serious infections (2%) vs. Placebo (< 1%) in clinical trials in RA. Administration of KINERET in RA should be discontinued if a patient develops a serious infection. In KINERET treated NOMID and DIRA patients the risk of a disease flare when discontinuing KINERET treatment should be weighed against the potential risk of continued treatment. Treatment with KINERET should not be initiated in patients with active infections. The safety and efficacy of KINERET in immunosuppressed patients or in patients with chronic infections have not been evaluated. (…)
|                                   |                   |            |                   | 5.6 Neutrophil Count |
|                                   |                   |            |                   | Patients receiving KINERET may experience a decrease in neutrophil counts. Neutrophil counts should therefore be assessed prior to initiating KINERET treatment, and while receiving KINERET, monthly for 3 months, and thereafter quarterly for a period up to 1 year. In the placebo-controlled studies, 6% of RA patients receiving KINERET had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Nine KINERET-treated patients (0.4%) experienced neutropenia (ANC < 1 x 10^9/L). This is discussed in more detail in the Adverse Reactions (6) section. In 43 NOMID patients followed for up to 60 months 2 patients experienced neutropenia that resolved over time during continued KINERET treatment. [see Adverse Reactions (6.2)].
|                                   |                   |            |                   | 6 ADVERSE REACTIONS |
|                                   |                   |            |                   | 6.2 Clinical Study Experience in NOMID |
|                                   |                   |            |                   | The data described herein reflect an open-label study in 43 NOMID patients exposed to KINERET for up to 60 months adding up to a total exposure of 159.8 patient years. Patients were treated with a starting dose of 1 to 2 mg/kg/day and an average maintenance dose of 3-4 mg/kg/day adjusted depending on the severity of disease. Among pediatric NOMID patients, doses up to 7.6 mg/kg/day have been maintained for up to 15 months. (…) |
|                                   |                   |            |                   | 8 USE IN SPECIFIC POPULATIONS |
|                                   |                   |            |                   | 8.1 Pregnancy |
|                                   |                   |            |                   | Risk Summary |
|                                   |                   |            |                   | Available data from retrospective studies and case reports on KINERET use in pregnant women are insufficient to identify a drug associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. There are risks to the mother and fetus associated with active rheumatoid arthritis or Cryopyrin-Associated Periodic Syndromes (CAPS). In animal reproduction studies, subcutaneous administration of anakinra to pregnant rats and rabbits during organogenesis demonstrated no evidence of fetal harm at doses up to 25 times the maximum recommended human dose (MRHD). (…) Clinical Considerations Disease-associated maternal and/or embryofetal risk Published data suggest the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or CAPS is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (<2500 grams), and small for gestational age at birth. |
|                                   |                   |            |                   | 8.4 Pediatric Use |
|                                   |                   |            |                   | Neonatal-Onset Multisystem Inflammatory Disease (NOMID) |
|                                   |                   |            |                   | The NOMID study included 36 pediatric patients: 13 below 2 years, 18 between 2 and 11 years, and 5 between 12 and 17 years of age. A subcutaneous KINERET starting dose of 1–2 mg/kg/day was increased to four mg/kg/day after 1 week. The maximum maintenance dose of 3–4 mg/kg/day was achieved in all age groups. An average maintenance dose of 3 mg/kg/day was maintained for up to 6 months. In the placebo-controlled studies, 6% of RA patients receiving KINERET had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Nine KINERET-treated patients (0.4%) experienced neutropenia (ANC < 1 x 10^9/L). This is discussed in more detail in the Adverse Reactions (6) section. In 43 NOMID patients followed for up to 60 months 2 patients experienced neutropenia that resolved over time during continued KINERET treatment. [see Adverse Reactions (6.2)].
|                                   |                   |            |                   | 12 CLINICAL PHARMACOLOGY |
|                                   |                   |            |                   | 12.3 Pharmacokinetics |
|                                   |                   |            |                   | (…) In NOMID patients, at a median SC dose of 3 mg/kg once daily and a median treatment time of 3.5 years, the median (range) steady-state serum exposure of anakinra was Cmax 3628 (655–8511) ng/mL (n=16) and C24h 203 (53–1979) ng/mL (n=16). The median (range) half-life of anakinra was 5.7 (3.1–28.2) hours (n=12). There was no obvious gender difference. (…) |
|                                   |                   |            |                   | 14 CLINICAL STUDIES |
|                                   |                   |            |                   | 14.2 Clinical Studies in NOMID |
|                                   |                   |            |                   | The efficacy of KINERET was evaluated in a prospective, long-term, open-label and uncontrolled study which incorporated a withdrawal period in a subset of 11 patients. This study included 43 NOMID patients 0.7 to 46 years of age treated for up to 60 months. Patients were given an initial KINERET dose of 1–2.4 mg/kg body weight. During the study, the dose was adjusted by 0.5 to 1 mg/kg increments to a protocol-specified maximum of 10 mg/kg daily, titrated to control signs and symptoms of disease. The maximum dose actually studied was 7.6 mg/kg/day. The average maintenance dose was 3 to 6 mg/kg/day. In general, the dose was given once daily, but for some patients, the dose was split into twice daily administrations for better control of disease activity. |

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<th>Labeling Sections</th>
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<tbody>
<tr>
<td>Anifrolumab-fnia</td>
<td>Rheumatology</td>
<td>Gene Signature (IFN)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<tr>
<td>Anifrolumab</td>
<td>Rheumatology</td>
<td>ESR, PGR</td>
<td>Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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</tr>
</thead>
<tbody>
<tr>
<td>021912, 05/29/2019</td>
<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>In patients with SLE, following the administration of anifrolumab-fnia at 300 mg dose, via intravenous infusion every 4 weeks for 52 weeks, neutralization (≥80%) of a type I IFN gene signature was observed from Week 4 to Week 50 in blood samples of patients with elevated levels of type I IFN inducible genes and returned to baseline levels within 8 to 12 weeks following withdrawal of anifrolumab-fnia at the end of the 52-week treatment period. However, the clinical relevance of the type I IFN gene signature neutralization is unclear. In SLE patients with positive anti-dsDNA antibodies at baseline (Trials 2 and 3), treatment with anifrolumab-fnia 300 mg led to numerical reductions in anti-dsDNA antibodies over time through Week 52. In patients with low complement levels (C3 and C4), increases in complement levels were observed in patients receiving anifrolumab-fnia through Week 52. Specific Populations: There was no clinically meaningful difference in systemic clearance based on age, race, ethnicity, region, gender, IFN status or body weight, that requires dose adjustment. 14 CLINICAL STUDIES: Randomization was stratified by disease severity (SLEDAI-2K score at baseline, &lt;10 vs ≥10 points). OCS dose on Day 1 (&lt;10 mg/day vs ≥10 mg/day prednisone or equivalent) and interferon gene signature test results (high vs low). (…)</td>
</tr>
<tr>
<td>021912, 05/29/2019</td>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.</td>
</tr>
<tr>
<td>021438, 02/23/2017</td>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.7 Dosage Adjustments for Cytochrome P450 Considerations: Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking coconcurrent CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inhibitors (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABLIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inhibitor is withdrawn, ABLIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response. (See Table 2)</td>
</tr>
<tr>
<td>207533, 11/30/2018</td>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.4 Dose Adjustments for Cytochrome P450 Considerations: For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours. Drug Interaction Studies: Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors. (…) Studies in Specific Populations: Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with ABLIFY to achieve a favorable clinical response, it is recommended to reduce the dosage to one-quarter (25%) of the usual dose initially and then adjust to achieve a favorable clinical response. (See Figure 4 and 5)</td>
</tr>
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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
|                                        |      |                   |            | Clinical Pharmacology | • No dosage changes recommended for ARISTADA, if CYP 450 modulators are added for less than 2 weeks.  
• Make dose changes to ARISTADA if CYP 450 modulators are added for greater than 2 weeks. (See Table 4) |

#### 8 USE IN SPECIFIC POPULATIONS

**8.6 CYP2D6 Poor Metabolizers**

Dose adjustment is recommended in known CYP 2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

#### 12 CLINICAL PHARMACOLOGY

**12.3 Pharmacokinetics**

**Metabolism and Elimination**

(…) Elimination of aripiprazole is mainly through hepatic metabolism involving CYP 3A4 and CYP 2D6. Dosage adjustments are recommended in CYP 2D6 poor metabolizers due to high aripiprazole concentrations [see Dosage and Administration (2.4)]. (…)

**Drug Interactions**

No specific drug interaction studies have been performed with ARISTADA. The drug interaction data provided below is obtained from studies with oral aripiprazole.

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cm ax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP 2D6 and CYP 3A4 inhibitors. After oral administration, a 3-fold increase in mean Cm ax and AUC values at steady-state is expected in poor metabolizers of CYP 2D6 administered with strong CYP 3A4 inhibitors. (See Figure 1, 2, and 3)

**Specific Population Studies**

A population pharmacokinetic analysis showed no effect of sex, race or smoking on ARISTADA pharmacokinetics [see Use in Specific Populations (8.8)].

Exposures of aripiprazole and dehydro-aripiprazole using oral aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. (See Figure 4 and 5)

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*02/1248, 06/20/2019* | Arsenic Trioxide | Oncology | PML-RARA | Indications and Usage, Clinical Studies | 1. Newly-Diagnosed Low-Risk APL

TRISENOX is indicated in combination with retinoid for treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML-RAR-alpha gene expression.

1.2. Relapsed or Refractory APL

TRISENOX is indicated for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML-RAR-alpha gene expression.

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*02/2468, 11/02/2018* | Articaine and Epinephrine (1) | Anesthesiology | G6PD | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS

5. Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

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*02/2468, 11/02/2018* | Articaine and Epinephrine (2) | Anesthesiology | Non-specific Congenital Methemoglobinemia | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS

5. Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

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*76/1034, 01/21/2022* | Atezolizumab (1) | Oncology | CD274 (PD-L1) | Indications and Usage, Dosage and Administration | 1. Urothelial Carcinoma

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

• are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test [see Dosage and Administration (2.1)], or

• are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or

• have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

1.2 Non-Small Cell Lung Cancer

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- **TECENTRIQ**, as a single-agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥1% of tumor cells, as determined by an FDA-approved test [see Dosage and Administration (2.1)].

- **TECENTRIQ**, as a single-agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥50% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥10% of the tumor area [IC ≥10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations [see Dosage and Administration (2.1)].

**2 DOSAGE AND ADMINISTRATION**

2.1 Patient Selection for Treatment of Urothelial Carcinoma, Non-Small Cell Lung Cancer and Melanoma

Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with TECENTRIQ based on the PD-L1 expression on tumor-infiltrating immune cells [see Clinical Studies (14.1)].

Select patients with Stage II to IIIA non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on PD-L1 expression on tumor cells [see Clinical Studies (14.2)].

Select patients with first-line metastatic non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on the PD-L1 expression on tumor cells or on tumor-infiltrating immune cells [see Clinical Studies (14.2)]. Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma or non-small cell lung cancer are available at: http://www.fda.gov/CompanionDiagnostics.

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

Non-small Cell Lung Cancer (NSCLC)

IMPower110

The safety of TECENTRIQ was evaluated in IMPower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naive patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations. Patients received TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin with either pemetrexed or gemcitabine (n=263) until disease progression or unacceptable toxicity [see Clinical Studies (14.2)]. IMPower110 enrolled patients whose tumors express PD-L1 (PD-L1 stained ≥1% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥1% of the tumor area). The median duration of exposure to TECENTRIQ was 5.3 months (0 to 11.5 months).

Previously Treated Metastatic NSCLC

(…) The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see Clinical Studies (14.2)].

6.2 Immunogenicity

(…) Among 487 ADA-evaluable patients with NSCLC who received atezolizumab in IMPower010, 31% (n=152) tested positive for treatment-emergent ADA at one or more post-dose time points. Among 241 patients in the PD-L1 STANdardized % TC Stage II-IIIA population, 26% (n=67) tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to ADA-negative patients [see Clinical Pharmacology (12.3)]. There were insufficient numbers of patients and DFS events in the ADA-positive subgroup (19%; 39/207 by week 75) to determine whether ADA alters the efficacy of atezolizumab. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

**12 CLINICAL PHARMACOLOGY**

12.3 Pharmacokinetics

Specific Populations

Age (21–85 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m²), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or AST < 1.5 × ULN and any AST), level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab.

**14 CLINICAL STUDIES**

14.1 Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

(…) Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 119 patients, 27% were classified as having PD-L1 expression of ≥5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 96% had impaired renal function, 28% had an ECOG PS of 2, 10% had a hearing loss ≥ 25 dB, and 9% had Grades 2–4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 22. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%). (See Table 22) (…) Both cisplatin-eligible and cisplatin-ineligible patients are included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The independent Data Monitoring Committee (IDMC) for the study conducted a review of early data and found that

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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.

Blue text represents the most recent additions and/or changes since last posted version.
**Table of Pharmacogenomic Biomarkers in Drug Labeling**

**Last Updated: 12/2023**

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections Text‡</th>
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<tr>
<td><strong>Table 1</strong></td>
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<td><strong>Table 2</strong></td>
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- The efficacy of TECENTRIQ was evaluated in IMpower110 (NCT02409342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC whose tumors express PD-L1 (PD-L1 ≥ 1% TC, Stage II – IIIA NSCLC (n=229), the median DFS was not reached (95% CI: 0.60, 1.26). (See Figure 1) |
- The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization. Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous) and PD-L1 expression (TC ≥ 1% and any IC < 1% and IC ≥ 1%). Patients were randomized (1:1) to receive one of the following treatment arms: |
- **Arm A: TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity** |
- **Arm B: Platinum-based chemotherapy** |

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systemic immunosuppressive medications within 2 weeks prior to randomization, or clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions as seen on imaging. Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC0/1 vs. TC0/1/2 and IC2/3. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for determination of IGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.

The major efficacy outcome measures for comparison of Arms A and C were progression free survival (PFS) by RECIST v1.1 in the IGE-WT (patients with high expression of t-efector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT WT subpopulations and overall survival (OS) in the IGE-WT subpopulation. Additional efficacy outcome measures for comparison of Arms A and C or Arms A and C were PFS and OS in the ITT subpopulation, OS in the IGE-WT subpopulation, and ORR/DoR in the IGE-WT and ITT-WT subpopulations.

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the IGE-WT subpopulation and 447 were in the IGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31-85); 59% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m2 while the remaining 87% received paclitaxel at a dose of 200 mg/m2. Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the IGE-WT subpopulation were similar to the ITT subpopulation except for the absence of patients with EGFR- or ALK-positive NSCLC.

The trial demonstrated a statistically significant improvement in PFS in Arms A and C compared to the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 25 and Figure 3. (…) IMpower130

The efficacy of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130 (NCT02367781), a multicenter, randomized (2:1), open-label trial in patients with stage IV non-squamous NSCLC. Patients with Stage IV non-squamous NSCLC who had received prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor, if appropriate, were eligible. The trial excluded patients with history of autoimmune disease, administration of live attenuated vaccine within 28 days prior to randomization, administration of immunomodulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, and active or untreated CNS metastases. Randomization was stratified by sex, presence of liver metastases, and PD-L1 tumor expression according to the VENTANA PD-L1 (SP142) assay as follows: TC3 and any IC vs. TC0/1/2 and IC0/1 vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. (…) A total of 724 patients were enrolled; of these, 681 (94%) were in the ITT-WT population. The median age was 64 years (range: 18 to 88) and 59% were male. The majority of patients were White (90%), 2% were Black, 6% were Hispanic, and 1% were Asian. 52% of patients were male, 30% of patients were Asian, 13% were Hispanic, and 5% were Black. Baseline ECOG performance status was 0 (41%) or 1 (59%). Most patients were current or previous smokers (90%). PD-L1 tumor expression was TC0/1/2 and IC0/1 in 73%, TC3 and any IC in 14%; and TC0/1/2 and IC2/3 in 13%. Efficacy results for the ITT-WT population are presented in Table 28 and Figure 3. (…) Previously Treated Metastatic NSCLC

The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with locally advanced or metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disease, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppressive medications within 2 weeks prior to enrollment were ineligible. Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. nonsquamous).

Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 96 weeks and every 9 weeks thereafter. The major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PDL1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v1.1. Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1.

Nearly all (94%) had metastatic disease, 74% had non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors. (See Table 27 and Figure 5.) Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for prespecified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Table of Pharmacogenomic Biomarkers in Drug Labeling

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<td>Metastatic Chemotherapy-Naive Non-Squamous NSCLC</td>
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Blue text represents the most recent additions and/or changes since last posted version.
The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (IGE) status and ECOG performance status 0 or 1. (…) Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated for PD-L1 staining (SP142) for PD-L1 tumor expression at a central laboratory. Tumor tissue was collected at baseline for expression of IGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures. The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the IGE-WT (patients with high expression of T-effector gene signature [IGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the IGE population, OS in the IGE-WT subpopulation, and ORR/DOR in the IGE-WT and ITT-WT subpopulations. A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. (…) The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the IGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 26 and Figure 3. (…)

The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC ([WT]). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. Baseline ECOG performance status was 0 (43%) or 1 (57%). The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥50% or IC ≥10%; TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%. Among the 205 chemotherapy-naïve patients with stage IV NSCLC high PD-L1 expression (TC ≥ 1%), who had received no prior chemotherapy for metastatic disease, PD-L1 tumor status was determined based on immunohistochemistry (IHC) testing using the VENTANA PD-L1 (SP142) Assay. The evaluation of efficacy is based on the subgroup of patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) in the IGE-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the IGE population, OS in the IGE-WT subpopulation, and ORR/DOR in the IGE-WT and ITT-WT subpopulations. (…) Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 15%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC. (…)

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<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
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<td>1.2 Non-Small Cell Lung Cancer</td>
<td>• TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.</td>
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<td>• TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>The safety of TECENTRIQ was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naive patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations.</td>
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<td>The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥ 50% or IC ≥ 10%; TC ≥ 25% or IC ≥ 10%; and TC ≥ 1% or IC ≥ 1%.</td>
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<td>Among the 205 chemotherapy-naive patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or IC 10%) excluding those with EGFR or ALK genomic tumor aberrations, the median age was 65.0 years (range: 33 to 87), and 70% of patients were male. The majority of patients were White (82%) and Asian (17%). Baseline ECOG performance status was 0 (36%) or 1 (64%), 88% were current or previous smokers; and 76% of patients had non-squamous disease while 24% of patients had squamous disease. (See Table 24 and Figure 2) (…)</td>
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<td>(…) Tumor assessments were conducted every 6 weeks for the first 48 weeks, then every 9 weeks thereafter. Major efficacy outcome measures were PFS by RECIST v1.1 and OS in the subpopulation of patients evaluated for and documented to have no EGFR or ALK genomic tumor aberrations (ITT-WT). (…)</td>
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| 021411, 05/19/2017                     | Atomoxetine | Psychiatry | CYP2D6 | Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION  
2.4 Dosing in Specific Populations  
Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs. In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.  

2.5 12 Laboratory Tests  
Routine laboratory tests are not required. CYP2D6 metabolism. Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA (see Adverse Reactions (6.1)).  

2.5.1 Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients who are known to be CYP2D6 PMs  
Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4 hydroxyatomoxetine. Dosage adjustment of STRATTERA may be necessary when coadministered with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine) or when administered to CYP2D6 PMs. [See Dosage and Administration (2.4) and Drug Interactions (7.2)].  

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Child and Adolescent Clinical Trials  
(…) The following adverse reactions occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: insomnia (11% of PMs, 6% of EMs); weight decreased (7% of PMs, 4% of EMs); constipation (7% of PMs, 4% of EMs); depression (7% of PMs, 4% of EMs); diarrhea (7% of PMs, 4% of EMs); sweating (7% of PMs, 4% of EMs).  

Adult Clinical Trials  
(…) The following adverse events occurred in at least 2% of adult CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: vision blurred (4% of PMs, 1% of EMs); dry mouth (35% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs); decreased appetite (23% of PMs, 15% of EMs); hyperhidrosis (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of EMs).  

7 DRUG INTERACTIONS  
7.2 Effect of CYP2D6 Inhibitors on Atomoxetine  
In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and Css. max is about 3- to 4-fold greater than atomoxetine alone. In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.  

8 USE IN SPECIFIC POPULATIONS  
8.6 Hepatic Insufficiency  
Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency [see Dosage and Administration (2.3)].  

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<th>Biomarker†</th>
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</table>

#### 8.7 Renal Insufficiency

EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.

#### 8.9 Ethnic Origin

Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).

#### 12 CLINICAL PHARMACOLOGY

##### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

The effect of STRATTERA on QTc prolongation was evaluated in a randomized, double-blinded, positive-(moxifloxacin 400 mg) and placebo-controlled, cross-over study in healthy male CYP2D6 poor metabolizers. A total of 120 healthy subjects were administered STRATTERA (20 mg and 60 mg) twice daily for 7 days. No large changes in QTc interval (i.e., increases >60 msec from baseline, absolute QTc >480 msec) were observed in the study. However, small changes in QTc interval cannot be excluded from the current study, because the study failed to demonstrate assay sensitivity. There was a slight increase in QTc interval with increased atomoxetine concentration.

##### 12.3 Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. (…)

Absorption and distribution

Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (Cmax) are reached approximately 1 to 2 hours after dosing. (…)

Metabolism and elimination

Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary [see Warnings and Precautions (5.13)]. Atomoxetine did not inhibit or induce the CYP2D6 pathway. The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated.

4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, has substantially less pharmacological activity compared with atomoxetine and circulates in plasma in lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs). Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours). (…)

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<tr>
<td>209112, 07/08/2022</td>
<td>Ascorbic Acid</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Dosage and Administration, Warnings and Precautions, Adverse Reactions, Patient Counseling Information</td>
<td>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNING AND PRECAUTIONS reflects exposure to SCEMBLIX at 10 mg to 200 mg orally twice daily (between 0.25 to 5 times the recommended dosage for the 80 mg daily dosage and between 0.05 times and up to 5 recommended dosage for the 200 mg twice daily dosage) in 356 patients enrolled in one of two clinical trials; including patients with Ph+ CML in chronic phase (CP) receiving SCEMBLIX as monotherapy: study CABL001X2101 (ASCEMBL) and study CABL001X2101 (see Clinical Studies (14)). Among the 356 patients receiving SCEMBLIX, the median duration of exposure to SCEMBLIX was 89 weeks (range, 0.1 to 342 weeks). The clinical trial randomized and treated 232 patients with Ph+ CML-CP, previously treated with two or more TKIs to receive SCEMBLIX 40 mg twice daily or budesonid 500 mg once daily (ASCEMBL) [see Clinical Studies (14.1)]. The safety population (received at least 1 dose of SCEMBLIX) included 156 patients with Ph+ CML-CP, previously treated with two or more TKIs. Among patients who received SCEMBLIX, 83% were exposed for 24 weeks or longer and 67% were exposed for 48 weeks or longer. (see Tables 3 and 4) Adverse Reactions in Patients with Ph+ CML-CP, Previously Treated With Two or More TKIs. The single-arm clinical trial included patients with Ph+ CML-CP with the T315I mutation (see Clinical Studies (14.2)). The safety population (received at least 1 dose of SCEMBLIX) included 48 patients with Ph+ CML-CP with the T315I mutation who received 200 mg of SCEMBLIX twice daily. Among these patients, 83% were exposed for 24 weeks or longer and 75% were exposed for 46 weeks or longer. (see Tables 5 and 6) 8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use In the ASCEMBL study, 44 of the 233 (19%) patients were 65 years of age or older and 6 (2.6%) were 75 years of age or older. In the X2101 study, 16 of the 48 (33%) patients with the T315I mutation were 65 years of age or older and 4 (8%) were 75 years of age or older. Overall, no differences in safety or efficacy of SCEMBLIX were observed between patients 65 years of age or older compared to younger patients. There is an insufficient number of patients 75 years of age or older to assess whether there are differences in safety or efficacy. 14 CLINICAL STUDIES 14.1 Ph+ CML-CP, Previously Treated With Two or More TKIs. The efficacy of SCEMBLIX in the treatment of patients with Ph+ CML-CP, previously treated with two or more tyrosine kinase inhibitors was evaluated in a multi-center, randomized, active-controlled, and open-label study ASCEMBL (NCT 03106779). (see Table 8) 14.2 Ph+ CML-CP with the T315I mutation. The efficacy of SCEMBLIX in the treatment of patients with Ph+ CML-CP with the T315I mutation was evaluated in a multi-center open-label study CABL001X2101 (NCT02081378). Testing for T315I mutation utilized a qualitative p210 BCR-ABL mutation test using Sanger Sequencing. Efficacy was based on 45 patients with Ph+ CML-CP with the T315I mutation who received SCEMBLIX at a dose of 200 mg twice daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred. 2 DOSAGE AND ADMINISTRATION 2.3 Dosage Reductions in Specific Populations. Women who are pregnant or lactating and patients with glucose-6-dehydrogenase deficiency should not exceed the U.S. Recommended Dietary Allowance (RDA) or daily Adequate Intake (AI) level for ascorbic acid for their age group and condition [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.2)]. 5 WARNINGS AND PRECAUTIONS 5.2 Hemolysis in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency. Hemolysis has been reported with administration of ascorbic acid in patients with glucose-6-phosphate dehydrogenase deficiency. Patients with glucose-6-phosphate dehydrogenase deficiency may be at increased risk for severe hemolysis during treatment with ascorbic acid. Monitor hemoglobin and blood count and use a reduced dose of ASCOR in patients with glucose-6-phosphate dehydrogenase deficiency [see Dosage and Administration (2.3)]. Discontinue treatment with ASCOR if hemolysis is suspected and treat as needed. 6 ADVERSE REACTIONS. • Hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency [see Warnings and Precautions (5.2)]. (…) Acute and chronic oxalate nephropathy have occurred with prolonged administration of high doses of ascorbic acid [see Warnings and Precautions (5.1)]. In patients with glucose-6-phosphate dehydrogenase deficiency, severe hemolysis has occurred [see Warnings and Precautions (5.2)]. 17 PATIENT COUNSELING INFORMATION. • Inform patients with glucose-6-phosphate dehydrogenase deficiency that treatment with ASCOR may increase their risk of hemolysis [see Warnings and Precautions (5.2)].</td>
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<td>Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.8 Glucose-6-phosphate dehydrogenase (G-6-PD) Deficiency Since MovPrep contains sodium ascorbate and ascorbic acid, MovPrep should be used with caution in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, especially G-6-PD deficiency patients with an active infection, with a history of hemolysis, or taking concomitant medications known to precipitate hemolytic reactions. 6 ADVERSE REACTIONS Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency [see Warnings and Precautions (5.8)]</td>
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<tr>
<td>212608, 05/22/2023</td>
<td>Avapritinib (1)</td>
<td>Oncology</td>
<td>PDGFRA</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST) AYVAKIT is indicated for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations [see Dosage and Administration (2.1)].</td>
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<tr>
<td>212608, 05/22/2023</td>
<td>Avapritinib (2)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Advanced Systemic Mastocytosis The efficacy of AYVAKIT was demonstrated in EXPLORER (NCT02561186) and PATHFINDER (NCT03580655), two multi-center, single-arm, open-label clinical trials. Response-evaluable patients include those with a confirmed diagnosis of AdvSM per World Health Organization (WHO) and deemed evaluable by modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline as adjudicated by an independent central committee, who received at least 1 dose of AYVAKIT, had at least 2 post-baseline bone marrow assessments, and had been on study for at least 24 weeks, or had an end of study visit. All enrolled patients had an ECOG performance status (PS) of 0 to 3 and 91% had a platelet count of ≥ 50 x 10^9/L prior to initiation of therapy. The study population characteristics were median age of 67 years (range: 27 to 85 years), 58% were male, 98% were White, 47% were Hispanic, and 5% had metastatic disease. 53% had largest target lesion &gt;5 cm, and 96% with prior surgical resection. The median number of prior kinase inhibitors was 1 (range: 0 to 36). Efficacy results in patients with GIST harboring PDGFRA exon 18 mutations including the subgroup of patients with PDGFRA D842V mutations enrolled in NAVIGATOR are summarized in Table 5. (See Table 5)</td>
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<td>210238, 06/30/2019</td>
<td>Avatrombopag (1)</td>
<td>Hematology</td>
<td>F2 (Prothrombin)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and</td>
</tr>
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| 210238, 06/30/2019                      | Avatrombopag (2) | Hematology       | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Thrombotic/Thromboembolic Complications  
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 210238, 06/30/2019                      | Avatrombopag (3) | Hematology       | PROC | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Thrombotic/Thromboembolic Complications  
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 210238, 06/30/2019                      | Avatrombopag (4) | Hematology       | PROS1 | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Thrombotic/Thromboembolic Complications  
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 210238, 06/30/2019                      | Avatrombopag (5) | Hematology       | SERPINC1 (Antithrombin III) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Thrombotic/Thromboembolic Complications  
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 210238, 06/30/2019                      | Avatrombopag (6) | Hematology       | CYP2C9 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.5 Pharmacogenomics  
The CYP2C9*2 and CYP2C9*3 loss-of-function polymorphisms result in reduced CYP2C9 enzymatic activity. In a pooled pharmacogenomic analysis of avatrombopag studies, subjects heterozygous for CYP2C9 loss-of-function polymorphisms (intermediate metabolizers [n=24]) had approximately 1.4-fold higher exposure and subjects homozygous for CYP2C9 loss-of-function polymorphisms (poor metabolizers [n=2]) had approximately 2-fold higher exposure compared to subjects wild-type for CYP2C9 (normal metabolizers [n=94]). |
| 761049, 06/30/2020                      | Avelumab | Oncology | CD274 (PD-L1) | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Metastatic Merkel Cell Carcinoma  
(…). A total of 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive (2% of tumors cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCP) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCP. Efficacy results are presented in Table 6. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCP. |
| 761049, 06/30/2020                      | Avelumab | Oncology | CD274 (PD-L1) | Clinical Studies | 14.2 Locally Advanced or Metastatic Urothelial Carcinoma  
First-Line Maintenance Treatment of Urothelial Carcinoma  
(…). Fifty-six percent (56%) of patients received prior gemcitabine plus cisplatin. 38% of patients received prior gemcitabine plus carboplatin, and 6% of patients received prior gemcitabine plus cisplatin and gemcitabine plus carboplatin. Best response to first-line chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis for the chemotherapy-naive patients were visceral (55%) or nonvisceral (45%). Fifty-one (51%) of patients had PD-L1-negative tumors, 10% of patients had unknown PD-L1 tumor status. Six percent (6%) of patients received another PD-1/PD-L1 checkpoint inhibitor after discontinuation of treatment in the BAVENCIO plus BSC arm and 44% of patients in the BSC arm. |

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<td>050794, 05/20/2022</td>
<td>Azacitidine (1)</td>
<td>Oncology</td>
<td>CBL</td>
<td>Clinical Studies</td>
<td>The major efficacy outcome measure was overall survival (OS) in all randomized patients and patients with PD-L1-positive tumors. The trial demonstrated a statistically significant improvement in OS for patients randomized to BAVENCIO plus BSC as compared with BSC alone (Table 9 and Figure 1). Consistent results were observed across the pre-specified subgroup of CR/PD versus SD to first-line chemotherapy. In the prespecified endpoint of OS among patients with PD-L1-positive tumors (n=358, 51%), the hazard ratio was 0.56 (95% CI: 0.40, 0.79; 2-sided p-value &lt;0.001) for patients randomized to BAVENCIO plus BSC versus BSC alone. In an exploratory analysis of patients with PD-L1-negative tumors (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.16). Previously-Treated Urothelial Carcinoma Patients were included regardless of their PD-L1 status. (…) Efficacy results are presented in Table 10. The median time to response was 2.0 months (range: 1.3 to 11.0) among patients followed for either &gt; 13 weeks or &gt; 6 months. Using a clinical trial assay to assess PD-L1 staining, with 16% of patients not evaluable, there were no clear differences in response rates based on PD-L1 tumor expression. (…) 14.3 Advanced Renal Cell Carcinoma The efficacy and safety of BAVENCIO in combination with axitinib was demonstrated in the JAVELIN Renal 101 trial (NCT02684006), a randomized, multi-center, open-label study of BAVENCIO in combination with axitinib in 886 patients with untreated advanced RCC regardless of tumor PD-L1 expression [intent-to-treat (ITT) population]. (…) The major efficacy outcome measures were progression-free survival (PFS), as assessed by an IRC using RECIST v1.1 and overall survival (OS) in patients with PD-L1-positive tumors using a clinical trial assay (PD-L1 expression level ≥ 1%). Since PFS was statistically significant in patients with PD-L1-positive tumors [HR 0.61 (95% CI: 0.48, 0.79)], it was then tested in the ITT population and a statistically significant improvement in PFS in the ITT population was also demonstrated.</td>
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<td>050794, 05/20/2022</td>
<td>Azacitidine (2)</td>
<td>Oncology</td>
<td>PTPN11</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Juvenile Myelomonocytic Leukemia (JMML) AZA-JMML-001 (NCT02447666) was an international, multicenter, open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety, and activity of VIDAZA prior to hematopoietic stem cell transplantation (HSCT) in a total of 18 pediatric patients (median age of 2.1 years, range 0.2-6.9 years; 61% male; 89% white) with juvenile myelomonocytic leukemia (JMML). Patients with newly diagnosed JMML were included if they met the following criteria: diagnosis confirmed in peripheral blood and bone marrow and had one of the following: somatic mutation in PTPN11, KRAS, or NRAS and HbF % &gt; 5 x normal value for age, or clinical diagnosis of neurofibromatosis Type 1 (NF-1). Additionally, patients included had no CNS involvement, isolated extramedullary disease, or germline molecular aberrations in CBL, PTPN11, NRAS, or KRAS. Eighteen patients with JMML (13 PTPN11, 3 NRAS, 1 KRAS somatic mutations and 1 clinical diagnosis of neurofibromatosis type 1 [NF-1]) were enrolled. (…)</td>
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<td>RAS</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Juvenile Myelomonocytic Leukemia (JMML) AZA-JMML-001 (NCT02447666) was an international, multicenter, open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety, and activity of VIDAZA prior to hematopoietic stem cell transplantation (HSCT) in a total of 18 pediatric patients (median age of 2.1 years, range 0.2-6.9 years; 61% male; 89% white) with juvenile myelomonocytic leukemia (JMML). Patients with newly diagnosed JMML were included if they met the following criteria: diagnosis confirmed in peripheral blood and bone marrow and had one of the following: somatic mutation in PTPN11, KRAS, or NRAS and HbF % &gt; 5 x normal value for age, or clinical diagnosis of neurofibromatosis Type 1 (NF-1). Additionally, patients included had no CNS involvement, isolated extramedullary disease, or germline molecular aberrations in CBL, PTPN11, NRAS, or KRAS. Eighteen patients with JMML (13 PTPN11, 3 NRAS, 1 KRAS somatic mutations and 1 clinical diagnosis of neurofibromatosis type 1 [NF-1]) were enrolled. (…)</td>
</tr>
<tr>
<td>016324, 12/20/2018</td>
<td>Azathioprine (1)</td>
<td>Rheumatology</td>
<td>TPMT</td>
<td>Dosage and Administration Patients with TPMT and/or NUDT15 Deficiency Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). Homozygous deficiency in either TPMT or NUDT15 Because of the risk of increased toxicity, consider alternative therapies for patients who are known to have TPMT or NUDT15 deficiency (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). Heterozygous deficiency in TPMT and/or NUDT15 Because of the risk of increased toxicity, dose reduction is recommended in patients known to have heterozygous deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests).</td>
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**WARNINGS**

**Cytopenias**

TPMT or NUDT15 Deficiency

(…). Patients with thiopurine S-methyl transferase (TPMT) or nucleotide diphosphate (NDT15) deficiency may be at an increased risk of severe and life-threatening myelotoxicity if receiving conventional doses of IMURAN (see CLINICAL PHARMACOLOGY). Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine. In patients with severe myelosuppression, consider evaluation for TPMT and NUDT15 deficiency (see PRECAUTIONS: Laboratory Tests). Consider alternative therapy in patients with homozygous TPMT or NUDT15 deficiency and reduced dosages in patients with heterogeneous deficiency (see DOSAGE AND ADMINISTRATION).

**PRECAUTIONS**

TPMT and NUDT15 Testing: Consider genotyping or phenotyping patients for TPMT deficiency and genotyping for NUDT1 deficiency in patients with severe myelosuppression. TPMT and NUDT15 testing cannot substitute for complete blood count (CBC) monitoring in patients receiving IMURAN. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections). Drug Interactions

Use with Allopurinol: One of the pathways for inactivation of azathioprine is inhibited by allopurinol. Patients receiving IMURAN and allopurinol concurrently should have a dose reduction of IMURAN, to approximately 1/3 to 1/4 the usual dose. It is recommended that a further dose reduction or alternative therapies be considered for patients with low or absent TPMT activity receiving IMURAN and allopurinol because both TPMT and XO inactivation pathways are affected. See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS: Laboratory Tests and ADVERSE REACTIONS sections.

**ADVERSE REACTIONS**

Hematologic

(…). Patients with low or absent TPMT or NUDT15 activity are at increased risk for severe, life-threatening myelosuppression from IMURAN (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias and PRECAUTIONS: Laboratory Tests, DOSAGE AND ADMINISTRATION).

**CLINICAL PHARMACOLOGY**

(…). 6-MP undergoes two major inactivation routes. One is thiol methylation, which is catalyzed by the enzyme thiopurine Smethyltransferase (TPMT), to form the inactive metabolite methyl-6-MP (6-MeMP). Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) to form 6-thiouric acid. The nucleotide diphosphatase (NDT15) enzyme is involved in conversion of the 6-TGNs to inactive 6-TG monophosphates. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities. Genetic polymorphisms influence TPMT and NUDT15 activity. Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of 6-MP or azathioprine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. Because of the risk of toxicity, patients with TPMT or NUDT15 deficiency require alternative therapy or dose modification (see DOSAGE AND ADMINISTRATION).

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity. Genetic polymorphisms influence TPMT and NUDT15 activity. Approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. (…)

**DOSAGE AND ADMINISTRATION**

Patients with TPMT and/or NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests).

Homozygous deficiency in either TPMT or NUDT15

Because of the risk of increased toxicity, consider alternative therapies for patients who are known to have TPMT or NUDT15 deficiency (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests).

Heterozygous deficiency in TPMT and/or NUDT15

Because of the risk of increased toxicity, dosage reduction is recommended in patients known to have heterozygous deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests).

**WARNINGS**

Cytopenias

TPMT or NUDT15 Deficiency

(…). Patients with thiopurine S-methyl transferase (TPMT) or nucleotide diphosphate (NDT15) deficiency may be at an increased risk of severe and life-threatening myelotoxicity if receiving conventional doses of IMURAN (see CLINICAL PHARMACOLOGY). Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine. In patients with severe myelosuppression, consider evaluation for TPMT and NUDT15 deficiency.

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</table>
| 206256, 01/08/2020                      | Belinostat | Oncology | UGT1A1 | Dosage and Administration, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION  
2.3 Patients with Reduced UGT1A1 Activity  
Reduce the starting dose of Beleodaq to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele [see Clinical Pharmacology (12.5)]. |
| 215383, 12/14/2023                      | Belzutifan (I) | Oncology | CYP2C19 | Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS  
5.1 Anemia  
(….) Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Closely monitor patients who are dual UGT2B17 and CYP2C19 poor metabolizers due to potential increases in exposure that may increase the incidence or severity of anemia [see Clinical Pharmacology (12.5)].  
(….) |

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<tr>
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<td>Belzutifan (2)</td>
<td>Oncology</td>
<td>UGT2B17</td>
<td>Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>Patients who are dual UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of WELIREG. Closely monitor for adverse reactions in patients who are dual UGT2B17 and CYP2C19 poor metabolizers [see Warnings and Precautions (5), Adverse Reactions (6), Clinical Pharmacology (12.5)].</td>
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</tbody>
</table>

**12 CLINICAL PHARMAECOLOGY**

**12.3 Pharmacokinetics**

**Specific Populations**

Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC [see Clinical Pharmacology (12.5)].

**Drug Interaction Studies**

Clinical Studies and Model-Informed Approaches

Effect of Belzutifan on CYP3A Substrates: Coadministration of WELIREG 120 mg once daily with midazolam (a sensitive CYP3A4 substrate) decreased the midazolam AUC by 40% and the Cmax by 34%. Midazolam AUC is predicted to decrease up to 70% in patients with higher belzutifan concentrations (e.g., dual poor metabolizers) [see Clinical Pharmacology (12.5)].

**12.5 Pharmacogenomics**

Patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers have 2-, 1.6-, or 3.2-fold higher belzutifan steady state AUC0-24h (respectively) compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers [see Use in Specific Populations (8.7)].

UGT2B17 poor metabolizers who are homozygous for the UGT2B17*2 allele have no UGT2B17 enzyme activity. CYP2C19 poor metabolizers (such as *2/*2, *3/*3, *2/*3) have significantly reduced or absent CYP2C19 enzyme activity. Approximately 15% of White, 6% of Black or African American, and up to 77% of certain Asian populations are UGT2B17 poor metabolizers. Approximately 2% of White, 5% of Black or African American, and up to 19% of certain Asian populations are CYP2C19 poor metabolizers. Approximately 0.4% of White, 0.3% of Black or African American, and up to 15% of certain Asian populations are dual UGT2B17 and CYP2C19 poor metabolizers.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Anemia**

(…). Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Closely monitor patients who are dual UGT2B17 and CYP2C19 poor metabolizers due to potential increases in exposure that may increase the incidence or severity of anemia [see Clinical Pharmacology (12.5)].

(…)

**7 DRUG INTERACTIONS**

**7.2 Effect of WELIREG on Other Drugs**

Sensitive CYP3A4 Substrates

Coadministration of WELIREG with CYP3A substrates decreases concentrations of CYP3A substrates [see Clinical Pharmacology (12.3)], which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Avoid coadministration of WELIREG with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information.

**8 USE IN SPECIFIC POPULATIONS**

**8.8 Dual UGT2B17 and CYP2C19 Poor Metabolizers**

Patients who are dual UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of WELIREG. Closely monitor for adverse reactions in patients who are dual UGT2B17 and CYP2C19 poor metabolizers [see Warnings and Precautions (5), Adverse Reactions (6), Clinical Pharmacology (12.5)].

**12 CLINICAL PHARMAECOLOGY**

**12.3 Pharmacokinetics**

**Specific Populations**

Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC [see Clinical Pharmacology (12.5)].

**Drug Interaction Studies**

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**12.5 Pharmacogenomics**

Patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers have 2-, 1.6-, or 3.2-fold higher belzutifan steady state AUC0-24h (respectively) compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers [see Use in Specific Populations (8.7)].

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</table>
| 020576, 11/06/2018                    | Betaine | Inborn Errors of Metabolism | CBS, MMADHC, MTHFR (Homocystinuria Deficiency) | Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE

CYSTADANE® is indicated for the treatment of homocystinuria to decrease elevated homocysteine blood concentrations in pediatric and adult patients. Included within the category of homocystinuria are:

- Cystathionine beta-synthase (CBS) deficiency
- 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
- Cobalamin cofactor metabolism (cbl) defect

5 WARNINGS AND PRECAUTIONS

5.1 Hypermethioninemia in Patients with CBS Deficiency

Patients with hypermethioninemia due to cystathionine beta-synthase (CBS) deficiency may also have elevated plasma methionine concentrations. Treatment with CYSTADANE may further increase methionine concentrations due to the remethylation of homocysteine to methionine. Cerebral edema has been reported in patients with hypermethioninemia, including patients treated with CYSTADANE [see Adverse Reactions (6.2)]. Monitor plasma methionine concentrations in patients with CBS deficiency. Plasma methionine concentrations should be kept below 1,000 micromol/L through dietary modification and, if necessary, a reduction of CYSTADANE dosage.

12.2 Pharmacodynamics

CYSTADANE was observed to lower plasma homocysteine concentrations in three types of homocystinuria, including CBS deficiency; MTHFR deficiency; and cbl defect. Patients have taken CYSTADANE for many years without evidence of tolerance. There has been no demonstrated correlation between Betaine concentrations and homocysteine concentrations. In CBS-deficient patients, large increases in methionine concentrations over baseline have been observed. CYSTADANE has also been demonstrated to increase low plasma methionine and S-adenosylmethionine (SAM) concentrations in patients with MTHFR deficiency and cbl defect.

14 CLINICAL STUDIES

CYSTADANE was studied in a double-blind, placebo-controlled, crossover study in 6 patients (3 males and 3 females) with CBS deficiency, ages 7 to 32 years at enrollment. CYSTADANE was administered at a dosage of 3 grams twice daily, for 12 months. Plasma homocysteine concentrations were significantly reduced (p<0.01) compared to placebo. Plasma methionine concentrations were variable and not significantly different compared to placebo.

CYSTADANE has also been evaluated in observational studies without concurrent controls in patients with homocystinuria due to CBS deficiency, MTHFR deficiency, or cbl defect. A review of 16 case studies and the randomized controlled trial previously described was also conducted, and the data available for each study were summarized; however, no formal statistical analyses were performed. The studies included a total of 78 male and female patients with homocystinuria who were treated with CYSTADANE. This included 48 patients with CBS deficiency, 13 with MTHFR deficiency, and 11 with cbl defect, ranging in age from 24 days to 53 years. (…) |

<table>
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<tr>
<th>210486, 10/11/2023</th>
<th>Binimetinib (1)</th>
<th>Oncology</th>
<th>BRAF</th>
<th>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific</th>
</tr>
</thead>
</table>
| 1 INDICATIONS AND USAGE

1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

MEK/ERK is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)].

1.2 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

MEK/ERK is indicated, in combination with encorafenib, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)]. |

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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection</td>
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<td>BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma</td>
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<td>Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating MEKTOVI [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: [<a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>].</td>
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2.2 Interstitial Lung Disease in patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 2 patients (0.3%) developed interstitial lung disease (ILD), including pneumonitis. |

2.5 Ocular Toxicities |

5 WARNINGS AND PRECAUTIONS |

5.2 Rhabdomyolysis |

5.3 Ocular Toxicities |

5.4 Interstitial Lung Disease in patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 1 patient experienced RVO (0.1%). | |

5.5 Interstitial Lung Disease |

6 ADVERSE REACTIONS |

6.1 Clinical Trials Experience |

6.2 Rhabdomyolysis |

6.3 Ocular Toxicities |

7 USE IN SPECIFIC POPULATIONS |

8.5 Geriatric Use |

8.6 Adams (2012) |

8.7 Other causes |

8.8 Interstitial lung disease |

8.9 Ocular toxicities |

9 CLINICAL STUDIES |

9.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma |

9.2 BRAF V600E Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) |

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<td>12.3 Pharmacokinetics</td>
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<td>Effect of UGT1A1 Inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Simulations predict similar Cmax of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).</td>
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<td></td>
<td></td>
<td>(Philadelphia chromosome)</td>
<td>6.1 Clinical Trials Experience</td>
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<td>Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL</td>
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|                                        |      |                |           | The safety data described below reflect exposure to BLINCYTO in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO (n = 267) or standard of care (SOC) chemotherapy (n = 109). (…)
|                                        |      |                |           | 14 CLINICAL STUDIES |
|                                        |      |                |           | 14.1 MRD-positive B-cell Precursor ALL |
|                                        |      |                |           | TOWER Study: The efficacy of BLINCYTO was evaluated in an open-label, multicenter, single-arm study (TOWER Study) [NCT02013167]. Eligible patients were ≥ 16 years of age with relapsed or refractory B-cell precursor ALL with ≥ 5% blasts in bone marrow and refractory to primary induction therapy or refractory to last therapy, untreated first relapse with first remission duration ≤ 12 months, untreated second or later relapse, or relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT). (See Table 11) (…)
|                                        |      |                |           | 14.2 Relapsed/Refractory B-cell Precursor ALL |
|                                        |      |                |           | TOWER Study: The efficacy of BLINCYTO was compared to standard care (SOC) chemotherapy in a randomized, open-label, multicenter study (TOWER Study) [NCT02013167]. Eligible patients were ≥ 16 years of age with relapsed or refractory B-cell precursor ALL with ≥ 5% blasts in bone marrow and refractory to primary induction therapy or refractory to last therapy, untreated first relapse with first remission duration ≤ 12 months, untreated second or later relapse, or relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT). (See Table 11) (…)
|                                        |      |                |           | 14.3 MRD-positive B-cell Precursor ALL |
|                                        |      |                |           | PHASER Study: The efficacy of BLINCYTO was evaluated in a phase II, open-label, multicenter, single-arm study (PHASER Study) [NCT02013167]. Eligible patients were ≥ 16 years of age with relapsed or refractory B-cell precursor ALL with ≥ 5% blasts in bone marrow and refractory to primary induction therapy or refractory to last therapy, untreated first relapse with first remission duration ≤ 12 months, untreated second or later relapse, or relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT). (See Table 11) (…)
|                                        |      |                |           | 14.4 MRD-positive B-cell Precursor ALL |
|                                        |      |                |           | CML-1 Study: The efficacy of BLINCYTO was evaluated in a phase II, open-label, multicenter, single-arm study (CML-1 Study) [NCT02013167]. Eligible patients were ≥ 16 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL or relapsed or refractory to at least 1 second generation or later tyrosine kinase inhibitor (TKI), or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate. (See Table 17) (…)
| 125557, 03/11/2021                     | Blinatumomab (2) | Oncology       | CD19      | 1 INDICATIONS AND USAGE |
|                                        |      |                |           | 1.1 MRD-positive B-cell Precursor ALL |
|                                        |      |                |           | BLINCYTO is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. |
|                                        |      |                |           | 1.2 Relapsed or Refractory B-cell Precursor ALL |
|                                        |      |                |           | BLINCYTO is indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children. |
| 202258, 01/30/2017                     | Boceprevir | Infectious Diseases | IFNL3 (IL28B) | 12 CLINICAL PHARMACOLOGY |
|                                        |      |                |           | 12.5 Pharmacogenomics |

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| 203341, 09/26/2023                    | Bosutinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | BOSULIF is indicated for the treatment of:  
- Adult and pediatric patients 1 year of age and older with chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML), newly-diagnosed or resistant or intolerant to prior therapy (see Clinical Studies (14.1, 14.2, 14.3)).  
- Adult patients with accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy (see Clinical Studies (14.2)). |

1 INDICATIONS AND USAGE

BOSULIF is indicated for the treatment of:
- Adult and pediatric patients 1 year of age and older with chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML), newly-diagnosed or resistant or intolerant to prior therapy (see Clinical Studies (14.1, 14.2, 14.3)).  
- Adult patients with accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy (see Clinical Studies (14.2)).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Dosage in Adult Patients with Newly-Diagnosed CP Ph+ CML

The recommended dosage of BOSULIF is 400 mg orally once daily with food.

Dosage in Adult Patients with CP, AP, or BP Ph+ CML with Resistance or Intolerance to Prior Therapy

The recommended dosage of BOSULIF is 500 mg orally once daily with food.

Dosage in Pediatric Patients with Newly-Diagnosed CP Ph+ CML or with CP Ph+ CML with Resistance or Intolerance to Prior Therapy

The recommended dosage of BOSULIF is 500 mg orally once daily with food.

2.2 Dose Escalation

In clinical studies of adult patients with Ph+ CML, dose escalation by increments of 100 mg once daily to a maximum of 600 mg once daily was allowed in patients who did not achieve or maintain a hematologic, cytogenetic, or molecular response and who did not have Grade 3 or higher adverse reactions at the recommended starting dosage. In pediatric patients with BSA <1.1 m2 and an insufficient response after 3 months consider increasing dose by 50 mg increments up to maximum of 100 mg above starting dose. Dose increases for insufficient response in pediatric patients with BSA ≥1.1 m2 can be conducted similarly to adult recommendations in 100 mg increments. The maximum dose in pediatric and adult patients is 600 mg once daily.

2.5 Dose Adjustments for Renal Impairment or Hepatic Impairment

The recommended starting doses for patients with renal and hepatic impairment are described in Table 4 below. (See Table 4)

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, and abdominal pain occur with BOSULIF treatment. Monitor and manage patients using standards of care, including anti-diarrheals, antiemetics, and fluid replacement. In the randomized clinical trial in patients with newly-diagnosed Ph+ CML, the median time to onset for diarrhea (all grades) was 3 days and the median duration per event was 3 days. Among 49 pediatric patients with newly-diagnosed CP Ph+ CML, or who had CP Ph+ CML that was resistant or intolerant to prior therapy, the median time to onset for diarrhea (all grades) was 2 days and the duration was 2 days. Among patients who experienced diarrhea, the median number of episodes of diarrhea per patient during treatment with BOSULIF was 2 (range 1 – 198). (…)

5.3 Hepatic Toxicity

(…) Among 49 pediatric patients with newly-diagnosed CP Ph+ CML or who had CP Ph+ CML that was resistant or intolerant to prior therapy, the incidence based on laboratory data that worsened from baseline of increased ALT was 59% and of increased AST 51%. Seventy-six percent of the patients experienced an increase in either ALT or AST. Most cases of increased transaminases occurred early in treatment; of patients who experienced increased transaminases of any grade, 84% of patients experienced their first increases within the first 3 months. The median time to onset for adverse reactions of increased ALT and AST was 22 and 15 days, respectively. The median duration for adverse reactions of Grade 3 or 4 increased ALT or AST was 26 and 12 days, respectively.

5.4 Cardiovascular Toxicity

(…) Among 49 pediatric patients with newly-diagnosed CP Ph+ CML or who had CP Ph+ CML that was resistant or intolerant to prior therapy, 4 (8%) patients had Grade 1-2 cardiac events, including tachycardia (n=2), angina pectoris, right bundle branch block, and sinus tachycardia (n=1 each).

5.4 Fluid Retention

Among 546 adult patients in a single-arm study in patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3 or 4 fluid retention was reported in 30 patients (6%). Some patients experienced more than one fluid retention event. Specifically, 24 patients experienced Grade 3 or 4 pleural effusions, 9 patients experienced Grade 3 or Grade 4 pericardial effusions, and 6 patients experienced Grade 3 edema. Among 49 pediatric patients with newly-diagnosed CP Ph+ CML or who had CP Ph+ CML that was resistant or intolerant to prior therapy, Grade 1-2 pericardial effusion, peripheral edema, and facial edema were reported in 1 patient each.

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</table>

5.6 Renal Toxicity  
Overall, 45% of the pediatric patients with newly diagnosed CP Ph+ CML or resistant or intolerant CP Ph+ CML who had normal eGFR at baseline shifted to a maximum of mild, and 40% pediatric patients who had mild eGFR at baseline shifted to a maximum of moderate during treatment.

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
The most common adverse reactions, in ≥20% of adults with newly diagnosed CP Ph+ CML or CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy (N=814) were diarrhea (8%), rash (4%), nausea (4%), abdominal pain (4%), vomiting (3%), fatigue (3%), hepatic dysfunction (3%), respiratory tract infection (2%), pyrexia (2%), and headache (2%).

8 USE IN SPECIFIC POPULATIONS  
8.4 Pediatric Use  
The safety and effectiveness of BOSULIF have been established in pediatric patients 1 year of age and older with newly-diagnosed CP Ph+ CML and CP Ph+ CML that is resistant or intolerant to prior therapy.

8.5 Geriatric Use  
In the Phase 1/2 clinical trial of BOSULIF in patients with Ph+ CML, 20% were age 65 and over, and 4% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

14 CLINICAL STUDIES  
14.1 Adult Patients with Newly-Diagnosed CP Ph+ CML  
The efficacy of BOSULIF in patients with newly-diagnosed chronic phase Ph+ CML was evaluated in the Bosutinib trial in First-line chronic myelogenous leukemia (BFORE) Trial: “A Multicenter Phase 3, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia” [NCT01309537].

The BFORE trial is a 2-arm, open-label, randomized, multicenter trial conducted to investigate the efficacy and safety of BOSULIF 400 mg once daily alone compared with imatinib 400 mg once daily in adult patients with newly-diagnosed CP Ph+ CML. The trial randomized 536 patients (268 in each arm) with Ph+ or Ph- newly-diagnosed CP CML, with intent-to-treat (ITT) population (imatinib) and baseline BCR-ABL copies >0 (modified intent-to-treat [mITT] population) including 487 patients with Ph+ CML harboring b2a2 and/or b3a2 transcripts at baseline and baseline BCR-ABL copies >0 (modified intent-to-treat [mITT] population). (…)

14.2 Adult Patients with Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML  
Study 200 (NCT00261846), a single-arm, open-label, multicenter study in patients with CML who were resistant or intolerant to prior therapy was conducted to evaluate the efficacy and safety of BOSULIF 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for CP, AP, and BP disease (…)

14.3 Pediatric Patients with Newly-Diagnosed CP Ph+ CML or with CP Ph+ CML with Resistance or Intolerance to Prior Therapy  
The efficacy of BOSULIF in pediatric patients with newly-diagnosed (ND) chronic phase (CP) Ph+ CML and patients with resistant/intolerant (R/i) CP Ph+ CML was evaluated in the BCHILD trial [NCT04258943]. The BCHILD trial is a multicenter, non-randomized, open-label study conducted to identify a recommended dose of bosutinib administered orally once daily in pediatric patients with ND CP Ph+ CML and pediatric patients with R/i CP Ph+ CML who have received at least one prior TKI therapy, to estimate the safety and tolerability, and efficacy, and to evaluate the PK of bosutinib in this patient population. The study enrolled 28 patients with R/i CP Ph+ CML treated with BOSULIF at 300 mg/m2 to 400 mg/m2 orally once daily, and 21 patients with ND CP Ph+ CML treated at 300 mg/m2 orally once daily. Efficacy outcomes included CCyR (defined as the absence of Ph+ metaphases in chromosome banding analysis of 50 metaphases, or <1% BCR-ABL1-positive nuclei of at least 200 peripheral blood interphase nuclei analyzed by Fluorescence In Situ Hybridization [FISH], or MMR if an adequate cytogenetic assessment was unavailable). CCyR (defined as CCyR or partial cytogenetic response of 1% to 35% Ph+ metaphases), and MMR (defined as ≥0.1% BCR-ABL1 ratio on international scale [IS]) at any time on study.

Patients with ND CP Ph+ CML had a median age of 14 years (range 5 to 17 years): 68% were male; 81% were White, 14% were Black/African American, and 5% were race not reported.

The major (MCyR) and complete (CCyR) cytogenetic responses among patients with ND CP Ph+ CML were 76.2% (95% CI: 52.8, 91.8) and 71.4% (95% CI: 14.3 L/h/m2 ) was 29% higher than BSA-normalized apparent clearance in adult patients with CP Ph+ CML (109.2 L/h/m2 ) [see Clinical Pharmacology (12.3)].

The safety and effectiveness of BOSULIF in pediatric patients younger than 1 year of age with newly diagnosed CP Ph+ CML, pediatric patients younger than 1 year of age with CP Ph+ CML that is resistant or intolerant to prior therapy, and pediatric patients with AP Ph+ CML or BP Ph+ CML have not been established.

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<td>Brentuximab Vedotin (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Use in Specific Populations, Clinical Studies</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.4 Pediatric Use</td>
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<td>The safety and effectiveness of ADCETRIS in combination with alternating chemotherapy Courses A (dexamethasone, ifosfamide, methotrexate, etoposide, cytarabine) and B (dexamethasone, methotrexate, cyclophosphamide, doxorubicin) administered every 21 days for a total of 6 cycles was assessed but have not been established based on a study (NCT01979536) in 67 patients, which included 61 pediatric patients age 2 to 17 with newly diagnosed ALK+ ALCL. No new safety signals were identified in this study.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.2 Systemic Anaplastic Large Cell Lymphoma and Other CD30-Expressing Peripheral T-Cell Lymphomas</td>
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<td>Randomized Clinical Trial in Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6: ECHELON-2, NCT01777152)</td>
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</tbody>
</table>
|                                        |      |                  |            |                  | The median age was 58 years (range: 18 to 85), 63% were male, 62% were White, 22% were Asian, and 78% had an ECOG performance status of 0-1. Of the 452 patients enrolled, the disease subtypes included patients with systemic ALCL (70; 48% anaplastic lymphoma kinase (ALK) negative and 22% ALK positive), PTCL not otherwise specified (63%), angioimmunoblastic T-cell lymphoma (12%), indolent lymphoma, chronic lymphocytic leukemia (3%), and enteropathy-associated T-cell lymphoma (1%). Most patients had Stage III or IV disease (81%) and a baseline international prognostic index of 2 or 3 (63%). (…)
|                                        |      |                  |            |                  | 14.3 Systemic Anaplastic Large Cell Lymphoma Clinical Trial in Relapsed ALCL (Study 2) |
|                                        |      |                  |            |                  | (…) The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 25% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative. (…)
| 125388, 11/10/2022                     | Brentuximab Vedotin (2) | Oncology | TNFRSF8 (CD230) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE |
|                                        |      |                  |            |                  | 1.5 Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), in combination with chemotherapy |
|                                        |      |                  |            |                  | ADCETRIS is indicated for the treatment of adult patients with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone. |
|                                        |      |                  |            |                  | 1.7 Relapsed primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30- expressing mycosis fungoides (MF) |
|                                        |      |                  |            |                  | ADCETRIS is indicated for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy. |
|                                        |      |                  |            |                  | 2 DOSAGE AND ADMINISTRATION |
|                                        |      |                  |            |                  | 2.1 Recommended Dosage |
|                                        |      |                  |            |                  | For dosing instructions of combination agents administered with ADCETRIS, see Clinical Studies (14.1 and 14.2) and the manufacturer’s prescribing information. (See Table 1) |
|                                        |      |                  |            |                  | 6 ADVERSE REACTIONS |
|                                        |      |                  |            |                  | 6.1 Clinical Trial Experience |
|                                        |      |                  |            |                  | (…) Data summarizing ADCETRIS exposure are also provided for 347 patients with T-cell lymphoma, including 223 patients with PTCL who received ADCETRIS in combination with chemotherapy in a randomized, double-blind, controlled trial: 58 patients with sALCL, who received ADCETRIS monotherapy in a single-arm trial; and 66 patients with pcALCL or CD30-expressing MF who received ADCETRIS monotherapy in a randomized, controlled trial. (…)
|                                        |      |                  |            |                  | Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6: ECHELON-2) |
|                                        |      |                  |            |                  | ADCETRIS in combination with CHP was evaluated in patients with previously untreated, CD30- expressing PTCL in a multicenter randomized, double-blind, double dummy, actively controlled trial. (See Table 7) (…)
|                                        |      |                  |            |                  | Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides (Study 4: ALCANZA) |
|                                        |      |                  |            |                  | ADCETRIS was studied in 131 patients with pcALCL or CD30-expressing MF requiring systemic therapy in a randomized, open-label, multicenter clinical trial in which the recommended starting dose and schedule was ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician’s choice of either methotrexate 5 to 50 mg orally weekly or bexarotene 300 mg/m2 orally daily. (See Table 10) (…)
|                                        |      |                  |            |                  | 8 USE IN SPECIFIC POPULATIONS |
|                                        |      |                  |            |                  | 8.5 Geriatric Use |
|                                        |      |                  |            |                  | (…) In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHELON-2), 31% of ADCETRIS + CHP-treated patients were age 65 or older. (…)

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### 14 CLINICAL STUDIES

14.2 Systemic Anaplastic Large Cell Lymphoma and Other CD30-Expressing Peripheral T-Cell Lymphomas

Randomized Clinical Trial in Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6: ECHELON-2, NCT0177152)

The efficacy of ADCETRIS in combination with chemotherapy for the treatment of adult patients with previously untreated, CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. For enrollment, the trial required CD30 expression ≥10% by immunohistochemistry. The trial excluded patients with primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. (See Table 13)

14.4 Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides

Randomized Clinical Trial in Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA, NCT01576499)

The efficacy of ADCETRIS in patients with primary cutaneous anaplastic large cell lymphoma (paALCL) or mycosis fungoides (MF) requiring systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. (…) Patients with paALCL must have received prior radiation or systemic therapy, and must have at least 1 biopsy with CD30-expression of ≥10%. Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30-expression of ≥10% in at least 1 biopsy. A total of 131 patients were randomized (66 ADCETRIS, 65 physician’s choice). The efficacy results were based on 128 patients (64 patients in each arm with CD30-expression of ≥10% in at least one biopsy). (See Table 17) (…) Supportive trials include 2 single-arm trials, which enrolled patients with MF who were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Out of 73 patients with MF from the 2 pooled supportive trials, 34% (25/73) achieved ORR4. Among these 73 patients, 35 had 1% to 9% CD30-expression and 31% (11/35) achieved ORR4.

### 205422, 02/09/2018

**Brexpiprazole** Psychiatry  

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<td><strong>2 DOSE AND ADMINISTRATION</strong></td>
<td><strong>2.5 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inhibitors or Inducers</strong></td>
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<tr>
<td>Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). If the coadministered drug is discontinued, adjust the REXULITI dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the REXULITI dosage to the original level over 1 to 2 weeks (see Drug Interactions [7.1], Clinical Pharmacology [12.3]). (See Table 1)</td>
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### 8 USE IN SPECIFIC POPULATIONS

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers, because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) (see Dosage and Administration (2.5), Clinical Pharmacology [12.3]).

### 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug interaction Studies

Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP3A4 inhibitors and CYP2D6 substrates and are classified as poor metabolizers of CYP2D6 (see Dosage and Administration (2.5), Clinical Pharmacology [12.3]).

### 208772, 05/22/2020

**Brigatinib** Oncology  

| ALK Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies |
|------------------------------------------|-------------------------------|
| **1 INDICATIONS AND USAGE** | **ALUNBRIG is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test [see Dosage and Administration (2.1)].** |
| **2 DOSE AND ADMINISTRATION** | **2.1 Patient Selection** |
| Select patients for the treatment of metastatic NSCLC with ALUNBRIG based on the presence of ALK positivity in tumor specimens [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics. |

### 6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Advanced ALK-positive NSCLC Without Prior ALK-targeted Therapy

In ALTA 1L, the safety of ALUNBRIG was evaluated in 136 patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy [see Clinical Studies (14)]. (…) ALK-positive Advanced or Metastatic NSCLC Previously Treated with Crizotinib

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive NSCLC who received at least 1 dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. (…)

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<tr>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY  12.3 Pharmacokinetics Metabolism Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.</td>
</tr>
<tr>
<td>Bupivacaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.</td>
</tr>
<tr>
<td>Bupivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY  12.3 Pharmacokinetics Potential for WELL BUTRIN to Affect Other Drugs Drugs Metabolized by CYP2D6: In vitro, bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion 300 mg/day followed by a single dose of 50 mg desipramine increased the Cmax, AUC, and t1/2 of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied. (…)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>12 CLINICAL STUDIES (…) Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph) chromosome. Also, the so-called “juvenile” type of chronic myelogenous leukemia, typically occurring in young children and associated with the absence of a Philadelphia chromosome, responds poorly to busulfan. The drug is of no benefit in patients whose chronic myelogenous leukemia has entered a “blastic” phase. (…)</td>
</tr>
<tr>
<td>Cabotegravir and Rilpivirine (1)</td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Clinical Trials in Adults The efficacy of CABENUVA has been evaluated in two Phase 3 randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials: 1. Trial 201584 (FLAIR, NCT02938520). (n = 629): HIV-1–infected, antiretroviral treatment (ART)-naive subjects received a dolutegravir INSTI-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other NRTIs if subjects were HLA B*5701 positive). (…)</td>
</tr>
<tr>
<td>Cabotegravir and Rilpivirine (2)</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Specific Populations No clinically significant differences in the pharmacokinetics of cabotegravir or rilpivirine were observed based on age, sex, race/ethnicity, body mass index, or UGT1A1 polymorphisms.</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>Capecitabine (1)</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions, Clinical Pharmacology, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.2 Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with certain homozygous or compound heterozygous variants in the DPD gene known to result in complete or near complete absence of DPD activity (complete DPD deficiency) are at increased risk for fatal adverse reactions due to severe mucositis, diarrhea, neutropenia, and neurotoxicity. Patients with partial DPD activity (partial DPD deficiency) may also have increased risk of serious, including fatal, adverse reactions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>XELODA is not recommended for use in patients known to have certain homozygous or compound heterozygous DPYD variants that result in complete DPD deficiency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider testing for genetic variants of DPYD prior to initiating XELODA to reduce the risk of serious adverse reactions if the patient’s clinical status permits and based on clinical judgement (see Clinical Pharmacology (12.5)). Serious adverse reactions may still occur even if no DPYD variants are identified.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>An FDA-authorized test for the detection of genetic variants of DPYD to identify patients at risk of serious adverse reactions due to increased systemic exposure to XELODA is not currently available. Currently available tests used to identify DPYD variants may vary in accuracy and design (e.g., which DPYD variant(s) they identify).</td>
</tr>
</tbody>
</table>

**5 INDICATIONS AND USAGE**

1.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer

XELODA is indicated for the:

- treatment of adults with advanced or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen.
- treatment of adults with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease as a component of a combination regimen.

2.2 Recommended Dosage for Gastric, Esophageal, or Gastroesophageal Junction Cancer

The recommended dosage of XELODA for metastatic gastric or gastroesophageal junction cancer is:

- 625 mg/m² orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy.
- 850 mg/m² or 1,000 mg/m² orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m² administered intravenously on day 1 of each cycle. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

**17 PATIENT COUNSELING INFORMATION**

Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and discuss with your patient whether they should be tested for genetic variants of DPYD that are associated with an increased risk of serious adverse reactions from the use of XELODA. Advise patients to immediately contact their healthcare provider if symptoms of severe mucositis, diarrhea, neutropenia, and neurotoxicity occur (see Warnings and Precautions (5.2) and Clinical Pharmacology (12.5)).

**INDICATIONS AND USAGE**

- 1.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer
  - XELODA is indicated for the:
  - treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen.
  - treatment of adults with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease as a component of a combination regimen.

- 2 DOSAGE AND ADMINISTRATION
  - 2.2 Recommended Dosage for Gastric, Esophageal, or Gastroesophageal Junction Cancer
    - The recommended dosage of XELODA for metastatic gastric or gastroesophageal junction cancer is:
      - 625 mg/m² orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy.
      - 850 mg/m² or 1,000 mg/m² orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m² administered intravenously on day 1 of each cycle. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2023**

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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td></td>
<td><strong>Oncology</strong> CAPItello-291</td>
<td><strong>AKT1</strong></td>
<td><strong>1 INDICATIONS AND USAGE</strong> TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on or recurrence in one or more endocrine-based regimens in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.</td>
<td>The recommended dosage of XELODA for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma is 1,000 mg/m2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with cisplatin and trastuzumab. Refer to the Prescribing Information for agents used in combination for additional dosing information as appropriate.</td>
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<td>218197, 11/16/2023</td>
<td>Capivasertib (2)</td>
<td>Oncology</td>
<td>ESRB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.</td>
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<tr>
<td>218197, 11/16/2023</td>
<td>Capivasertib (3)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.</td>
</tr>
<tr>
<td>218197, 11/16/2023</td>
<td>Capivasertib (4)</td>
<td>Oncology</td>
<td>PIK3CA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
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<td></td>
</tr>
<tr>
<td>218197, 11/16/2023</td>
<td>Capivasertib (5)</td>
<td></td>
<td>PTEN</td>
<td></td>
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Information on FDA-approved tests for the detection of PIK3CA, AKT1, and PTEN alterations is available at: http://www.fda.gov/CompanionDiagnostics.

6 ADVERSE REACTIONS
CAPiello-291
The safety of TRUQAP was evaluated in CAPiello-291, a clinical trial including 288 adult patients (155 patients in TRUQAP with fulvestrant arm and 133 patients in placebo with fulvestrant arm) whose breast cancer had one or more PIK3CA/AKT1/PTEN-alterations [see Clinical Studies (14)]. Among patients who received TRUQAP, 61% were exposed for 6 months or longer and 30% were exposed for greater than one year. (…)

14 CLINICAL STUDIES
The efficacy of TRUQAP with fulvestrant was evaluated in CAPiello-291 (NCT04305496), a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 708 adult patients with locally advanced (inoperable) or metastatic HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+ or ISH+) breast cancer of which 289 patients had tumors with eligible PIK3CA/AKT1/PTEN-alterations. Eligible PIK3CA/AKT1 activating mutations or PTEN loss of function alterations were identified in the majority of FFPE tumor specimens using FoundationOneCDx next-generation sequencing (n=686). All patients were required to have progression on an aromatase inhibitor (AI) based treatment in the metastatic setting or recurrence on or within 12 months of completing neo/adjuvant treatment with an AI. Patients could have received up to two prior lines of endocrine therapy and up to 1 line of chemotherapy for locally advanced (inoperable) or metastatic disease. Patients were excluded if they had clinically significant abnormalities of glucose metabolism (defined as patients with diabetes mellitus Type 1, Type 2, requiring insulin treatment, or HbA1c 28% (6.9 mmol/mol)). Patients were randomized (1:1) to receive either 400 mg of TRUQAP (n=355) or placebo (n=330), given orally twice daily for 4 days followed by 3 days off treatment each week of 28-day treatment cycle. Fulvestrant 500 mg intramuscular injection was administered on cycle 1 days 1 and 15, and then at day 1 of each subsequent 28-day cycle. Patients were treated until disease progression, or unacceptable toxicity. Randomization was stratified by presence of liver metastases (yes vs. no), prior treatment with CDK4/6 inhibitors (yes vs. no) and geographical region (region 1: US, Canada, Western Europe, Australia, and Israel vs region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia).

The major efficacy outcomes were investigator-assessed progression-free survival (PFS) in the overall population, and in the population of patients whose tumors have PIK3CA/AKT1/PTEN-alterations evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). A statistically significant difference in PFS was observed in the overall population and the population of patients whose tumors have PIK3CA/AKT1/PTEN-alterations. An exploratory analysis of PFS in the 313 (44%) patients whose tumors did not have a PIK3CA/AKT1/PTEN-alteration showed a HR of 0.79 (95% CI: 0.61, 1.02), indicating that the difference in the overall population was primarily attributed to the results seen in the population of patients whose tumors have PIK3CA/AKT1/PTEN-alteration.

Of the 289 patients whose tumors were PIK3CA/AKT1/PTEN-altered, the median age was 59 years (range 34 to 90); female (99%), White (52%), Asian (29%), Black (1%), American Indian/Alaska Native (0.7%), other races (17%) and 9% were Hispanic/Latino. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (66%) or 1 (34%), and 18% were premenopausal or perimenopausal. Seventy-six percent of patients had an alteration in PIK3CA, 13% had an alteration in AKT1, and 17% had an alteration in PTEN. All patients received prior endocrine-based therapy (100% AI based treatment and 44% received tamoxifen). Seventy-one percent of patients were previously treated with a CDK4/6 inhibitor and 18% received prior chemotherapy for locally advanced (inoperable) or metastatic disease.

Efficacy results for PIK3CA/AKT1/PTEN-altered subgroup are presented in Table 7 and Figure 1. Results from the blinded independent review committee (BIRC) assessment were consistent with the investigator assessed PFS results. Overall survival results were immature at the time of the PFS analysis (30% of the patients died). (See Table 7 and Figure 1)

1 INDICATIONS AND USAGE
TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with TRUQAP, based on the presence of one or more of the following genetic alterations in tumor tissue: PIK3CA/AKT1/PTEN-alteration [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of PIK3CA, AKT1, and PTEN alterations is available at: http://www.fda.gov/CompanionDiagnostics.

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CAPiello-291
The safety of TRUQAP was evaluated in CAPiello-291, a clinical trial including 288 adult patients (155 patients in TRUQAP with fulvestrant arm and 133 patients in placebo with fulvestrant arm) whose breast cancer had one or more PIK3CA/AKT1/PTEN-alterations [see Clinical Studies (14)]. Among patients who received TRUQAP, 61% were exposed for 6 months or longer and 30% were exposed for greater than one year. (…)

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Of the 289 patients whose tumors were PIK3CA/AKT1/PTEN-altered, the median age was 59 years (range 34 to 90); female (99%); White (52%), Asian (29%), Black (1%), American Indian/Alaska Native (0.7%), other races (1%) and 9% were Hispanic/Latino. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (66%) or 1 (34%), and 18% were premenopausal or perimenopausal. Seventy-six percent of patients had an alteration in PIK3CA, 13% had an alteration in AKT1, and 17% had an alteration in PTEN. All patients received prior endocrine-based therapy (100% AI based treatment and 44% received tamoxifen). Seventy-one percent of patients were previously treated with a CDK4/6 inhibitor and 18% received prior chemotherapy for locally advanced (inoperable) or metastatic disease. Efficacy results for PIK3CA/AKT1/PTEN-altered subgroup are presented in Table 7 and Figure 1. Results from the blinded independent review committee (BIRC) assessment were consistent with the investigator assessed PFS results. Overall survival results were immature at the time of the PFS analysis (30% of the patients died). (See Table 7 and Figure 1.)

**1 INDICATIONS AND USAGE**

TABRECTA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved assay.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**

Select patients for treatment with TABRECTA based on the presence of a mutation that leads to MET exon 14 skipping in tumor or plasma specimens [see Clinical Studies (14)]. If a mutation that leads to MET exon 14 skipping is not detected in a plasma specimen, test tumor tissue if feasible. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

**14 CLINICAL STUDIES**

Metastatic NSCLC with a Mutation that Leads to MET Exon 14 Skipping

The efficacy of TABRECTA was evaluated in GEOMETRY mono-1, a multicenter, non-randomized, open-label, multicohort study (NCT02414139). Eligible patients were required to have NSCLC with a mutation that leads to MET exon 14 skipping, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with indeterminate or rare pharmacologic receptors, who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. Out of the 97 patients enrolled in GEOMETRY mono-1 following the central confirmation of MET exon 14 skipping by a RNA-based clinical trial assay, 78 patient samples were retested with the FDA-approved FoundationOne® CDx (22 treatment-naïve and 56 previously treated patients) to detect mutations that lead to MET exon 14 skipping. Out of 76 samples retested with FoundationOne® CDx, 73 samples were evaluable (20 treatment-naïve and 53 previously treated patients), 72 (20 treatment-naïve and 52 previously treated patients) of which were confirmed to have a mutation that leads to MET exon 14 skipping, demonstrating an estimated positive percentage agreement of 99% (72/73) between the clinical trial assay and the FDA-approved assay.

**Table of Pharmacogenomic Biomarkers in Drug Labeling**

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>03/2018, 213591, 08/10/2022</td>
<td>Capmatinib</td>
<td>Oncology</td>
<td>MET</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
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<tr>
<td>016608, 03/20/2018</td>
<td>Carbamazepine (1)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>BOXED WARNING</td>
</tr>
</tbody>
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| 016608, 03/20/2018                     | Carbamazepine (2) | Neurology | HLA-A | Warnings | Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with Tegretol treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Tegretol should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. SJS/TEN and HLA-B*1502 Allele

**Precautions**

For genetically at-risk patients (see WARNINGS), high-resolution ‘HLA-B*1502 typing’ is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

**Indications and Usage**

1.1 Acute hyperammonemia in patients with NAGS deficiency

Carbaglu is indicated as an adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During acute hyperammonemic episodes concomitant administration of Carbaglu with other ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction are recommended.

1.2 Chronic Hyperammonemia in Patients with NAGS Deficiency

Carbaglu is indicated for maintenance therapy in pediatric and adult patients for chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be reduced or discontinued based on plasma ammonia levels.

2. Dose and Administration

2.1 Recommended Dose

CARBAGLU should be initiated as soon as the diagnosis of NAGS deficiency is suspected, which may be as soon as at birth, and managed by a physician and medical team experienced in metabolic disorders. (…)

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</table>
| 04/04/2019 | 011792                | Cariprazine | Psychiatry | CYP2D6    | Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS
5.1 Hyperammonemia
(...)
Since hyperammonemia in NAGS deficiency is the result of imbalance between ammonia detoxification capacity and protein catabolism, complete protein restriction during an acute hyperammonemic episode is recommended for no longer than 12 to 36 hours while maximizing caloric supplementation to reverse catabolism. Protein should be reintroduced as early as possible, following improvement of metabolic and clinical abnormalities in this setting. During long-term management, dietary protein restriction should be instituted to maintain blood ammonia level within an acceptable range for age.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
There are no adequate and well controlled studies or available human data with Carbaglu in pregnant women. Decreased survival and growth occurred in offspring born to animals that received carylglicemic acid at doses similar to the maximum recommended starting human dose during pregnancy and lactation. Because untreated N-acetylglutamate synthase (NAGS) deficiency results in irreversible neurologic damage and death, women with NAGS must remain on treatment throughout pregnancy. (…)

8.3 Nursing Mothers
It is not known whether Carbaglu is excreted in human milk. Carylglumatic acid is excreted in rat milk, and an increase in mortality and impairment of body weight gain occurred in neonatal rats nursed by mothers receiving carylglicemic acid. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Carbaglu, human milk-feeding is not recommended. Treatment is continuous and life-long for NAGS deficiency patients.

8.4 Pediatric Use
The efficacy of Carbaglu for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began Carbaglu treatment during infancy or childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Carbaglu, however, data are limited.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
In a retrospective review of the clinical course in 23 patients with NAGS deficiency, carylglicemic acid reduced plasma ammonia levels within 24 hours when administered with and without concomitant ammonia lowering therapies. No dose response relationship has been identified. (…)

14 CLINICAL STUDIES
14.1 Responses of Patients with NAGS Deficiency to Acute and Chronic Treatment
The efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who received Carbaglu treatment for a median of 7.6 years (range 0.6 to 20.8 years). (See Table 2) (...)

12.3 Pharmacokinetics
CYP2D6 Poor Metabolizers
CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR. Drug Interaction Studies
CYP2D6 inhibitors
CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine. DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.

12.3 Pharmacokinetics
Metabolism
The major pathway of carylglicemic metabolism is via the liver by cytochrome enzyme CYP2C19 to form metcarylglicemic. This enzyme exhibits genetic polymorphism (see Patients with Reduced CYP2C19 Activity below). Patients with Reduced CYP2C19 Activity
SOMA should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carylglicemic and, concomitant 50% reduced exposure to metcarylglicemic compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.

12.3 Pharmacokinetics
Metabolism
The major pathway of carylglicemic metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism (see Patients with Reduced CYP2C19 Activity below). Patients with Reduced CYP2C19 Activity
SOMA should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carylglicemic and, concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.

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| 05/24/2019 | 204370                | Carisoprodol | Rheumatology | CYP2C19    | Use in Specific Populations, Clinical Pharmacology | 8 USE IN SPECIFIC POPULATION
8.8 Patients with Reduced CYP2C19 Activity
Patients with reduced CYP2C19 activity have higher exposure to carylglicemic. Therefore, caution should be exercised in administration of SOMA to these patients [see Clinical Pharmacology (12.3)].

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism
The major pathway of carylglicemic metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism (see Patients with Reduced CYP2C19 Activity below). Patients with Reduced CYP2C19 Activity
SOMA should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carylglicemic and, concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.

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<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
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<td>02/25/2021, 213026</td>
<td>Casimersen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
</tr>
</tbody>
</table>

1 INDICATIONS AND USAGE
AMONDYS 45 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS 45 [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
AMONDYS 45 is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping, including pediatric patients [see Clinical Studies (14)].

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
In the interim analysis of muscle biopsy tissue obtained at baseline and at Week 48 from patients in Study 1, patients who received AMONDYS 45 (n=27) demonstrated a significant increase in skipping of exon 45 (p<0.001) compared to baseline, demonstrated by reverse transcription digital droplet polymerase chain reaction (RT-ddPCR). Patients who received placebo (n=16) did not demonstrate a significant increase in exon 45 skipping (p=0.808). The level of exon skipping is positively correlated with dystrophin protein expression [see Clinical Studies (14)]. In Study 1 [see Clinical Studies (14)], dystrophin levels assessed by the Sarepta Western blot assay increased from 0.93% (SD 1.67) at normal baseline to 1.74% (SD 1.97) of normal after 48 weeks of treatment with AMONDYS 45. The mean change from baseline in dystrophin after 48 weeks of treatment with AMONDYS 45 was 0.81% (SD 0.70) of normal levels (p<0.001). This increase in dystrophin protein expression after treatment with AMONDYS 45 positively correlated with the level of exon skipping. The mean change from baseline in dystrophin after 48 weeks of treatment with placebo was 0.22% (SD 0.49). Patients who received AMONDYS 45 showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 compared to those who received placebo (mean difference of 0.59%; p = 0.004). Dystrophin levels assessed by Western blot can be meaningfully influenced by differences in sample processing, analytical technique, reference materials, and quantitation methodologies. Therefore, comparing dystrophin results from different assay protocols will require a standardized reference material and additional bridging studies. Correct localization of dystrophin to the sarcolemma in patients treated with AMONDYS 45 was demonstrated by immunofluorescence staining.

12.3 Pharmacokinetics
Specific Populations
Age, Sex & Race
The pharmacokinetics of AMONDYS 45 have been evaluated in male DMD patients 9 to 20 years of age. There is no experience with the use of AMONDYS 45 in DMD patients 65 years of age or older. AMONDYS 45 has not been studied in female patients. The potential impact of race on the pharmacokinetics of casimersen is unknown.

Patients with Renal Impairment
The effect of renal impairment on the pharmacokinetics of casimersen was evaluated in nonDMD subjects aged 35 to 65 years with Stage 2 chronic kidney disease (CKD) (n=8), estimated glomerular filtration rate (eGFR) ≤60 and <90mL/min/1.73 m² or Stage 3 CKD (n=8, eGFR ≤30 and <60mL/min/1.73 m²) and matched healthy subjects (n=8, eGFR ≥60 mL/min/1.73 m²). Subjects received a single 30 mg/kg intravenous dose of casimersen. In subjects with Stage 2 or Stage 3 CKD, exposure (AUC) increased approximately 1.2-fold and 1.8-fold, respectively, compared with subjects with normal renal function. The Cmax in subjects with Stage 2 CKD was similar to Cmax in subjects with normal renal function; in subjects with Stage 3 CKD, there was a 1.2-fold increase in AUC relative to subjects with normal renal function.

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<td>Celecoxib</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>Poor Metabolizers of CYP2C9 Substrates In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)].</td>
</tr>
</tbody>
</table>

### 14 CLINICAL STUDIES

The effect of AMONDYS 45 on dystrophin production was evaluated in one study in male DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping (Study 1; NCT02500381). (…)

### 8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see Poor Metabolizers of CYP2C9 substrates (8.8)].

8.8 Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), administer CELEBREX starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)].

### 12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.8)].

| 761097, 11/08/2022 | Cemiplimab-rwlc | Oncology | ALK | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE 1.3 Non-Small Cell Lung Cancer LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 aberrations and is: • locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or • metastatic. LIBTAYO as a single agent is indicated for the first-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR, ALK or ROS1 aberrations, and is: • locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or • metastatic. |

14 CLINICAL STUDIES

14.3 Non-Small Cell Lung Cancer (NSCLC)

First-line treatment of NSCLC with LIBTAYO in combination with platinum-based chemotherapy Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; autoimmune disease that required systemic therapy within 2 years of treatment; or who had never smoked were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization. (…)

| 761097, 11/08/2022 | Cemiplimab-rwlc | Oncology | CD274 (PD-L1) | Indications and Usage, Dosage and Administration | 1 INDICATIONS AND USAGE 1.3 Non-Small Cell Lung Cancer |

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increase in Cmax compared with subjects with normal renal function. The effect of Stage 4 or Stage 5 CKD on cemiplimab pharmacokinetics and safety has not been studied.

Estimated GFR values derived from MDRD equations and the threshold definitions for various CKD stages in otherwise healthy adults would not be generalizable to pediatric patients with DMD. Therefore, no specific dosage adjustment can be recommended for patients with renal impairment [see Use in Specific Populations (8.6)].

8.8 Poor Metabolizers of CYP2C9 Substrates In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), administer CELEBREX starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)].

Detailed pharmacokinetic data are not available in the pediatric population. In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)].

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.8)].

14 CLINICAL STUDIES

14.3 Non-Small Cell Lung Cancer (NSCLC)

First-line treatment of NSCLC with LIBTAYO in combination with platinum-based chemotherapy Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; autoimmune disease that required systemic therapy within 2 years of treatment; or who had never smoked were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization. (…)

First-line treatment of NSCLC with LIBTAYO as a single agent Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; autoimmune disease that required systemic therapy within 2 years of treatment; or who had never smoked were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization. (…)

1 INDICATIONS AND USAGE 1.3 Non-Small Cell Lung Cancer LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 aberrations and is: • locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or • metastatic. LIBTAYO as a single agent is indicated for the first-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR, ALK or ROS1 aberrations, and is: • locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or • metastatic.
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<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Clinical Studies</td>
<td>LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR, ALK or ROS1 aberrations, and is: locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.</td>
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<td>761097, 11/08/2022</td>
<td>Gemcitabine-rwlc (4)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.3 Non-Small Cell Lung Cancer LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 aberrations and is: locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic: LIBTAYO as a single agent is indicated for the first-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR, ALK or ROS1 aberrations, and is: locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.</td>
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<td>Ceftriaxone (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings</td>
<td>Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<tr>
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<td>Infectious Diseases</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>205755, 03/05/2019</td>
<td>Ceritinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Warnings</td>
<td>1 INDICATIONS AND USAGE ZYKADIA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.</td>
</tr>
</tbody>
</table>

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</table>
| **14.2 Previously Treated ALK-Positive Metastatic NSCLC** | 761052, 12/06/2019 | Cerliponase Alfa Inborn Errors of Metabolism | TPP1 Indications and Usage, Use in Specific Populations, Clinical Studies | The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (ASCEND-1, NCT01283516). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily. The study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (92%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastases included brain (60%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients. (…)

**8 USE IN SPECIFIC POPULATIONS**

**8.4 Pediatric Use**
Safety and effectiveness of Brineura have been established in pediatric patients 3 years of age and older. Pediatric use of Brineura to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, compared to untreated patients with CLN2 disease from an independent natural history cohort (see Clinical Studies (14)). Safety and effectiveness in patients less than 3 years of age have not been established.

**14 CLINICAL STUDIES**

The efficacy of Brineura was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency. (…)

(…) Motor scores of the 22 Brineura-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study. The results of logistic modeling with covariates (screening age, screening motor score, genotype: 0 key mutations (yes/no)), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% CI): 13.1 (1.2, 146.9)). (…) Descriptive non-randomized comparison

(…) Given the non-randomized study design, a Cox Proportional Hazards Model adjusted for age, initial motor score, and genotype was used to evaluate time to unreversed 2-category decline or unreversed score of 0 in the Motor domain. This model showed a lesser decrease in motor function in the Brineura-treated patients compared to the natural history cohort (see Figure 7). Motor Domain Scores: Matched Patients Only

(…) To further assess efficacy, the 22 patients from the Brineura clinical study with a baseline combined Motor plus Language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. Patients were matched based on the following covariates: baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening. (see Table 3) (…)

| 125084, 09/24/2021 | Cetuximab (1) | Oncology | EGFR Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | The efficacy of ERBITUX is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test (see Dosage and Administration (2.2)): (…) in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment, (…) in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, (…) as a single-agent in patients who have failed oxalaplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when he results of the Ras mutation tests are unknown (see Warnings and Precautions (5.7), Clinical Studies (14.2)).

**2 DOSAGE AND ADMINISTRATION**

2.1 Patient Selection
Select patients with metastatic colorectal cancer (CRC) for treatment with ERBITUX based on the presence of:

• Ras wild-type, EGFR-expressing CRC (see Clinical Studies (14.2)), or
• BRAF V600E mutation-positive metastatic CRC (see 14.3) Information on FDA-approved tests for the detection of K-Ras or BRAF V600E mutations in CRC in patients with metastatic CRC is available at: http://www.fda.gov/CompanionDiagnostics.

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience
K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)
In Combination with FOLFIRI
(…) The safety of a cetuximab product in combination with FOLFIRI or FOLFOX alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…) As Monotherapy

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</table>
| 125084, 09/24/2021                    | Cetuximab (2) | Oncology | RAS | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer  
ERBITUX is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test [see Dosage and Administration (2.2)];  
• in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment,  
• in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,  
• as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

5 WARNINGS AND PRECAUTIONS  
5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC  
Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when he results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Select patients with metastatic colorectal cancer (CRC) for treatment with ERBITUX based on the presence of:  
• Ras wild-type, EGFR-expressing CRC [see Clinical Studies (14.2)], or  
• BRAF V600E mutation-positive metastatic CRC [see Clinical Studies (14.3)] Information on FDA-approved tests for the detection of K-Ras or BRAF V600E mutations in CRC in patients with metastatic CRC is available at: http://www.fda.gov/CompanionDiagnostics.

5.7 WARNING AND PRECAUTIONS  
5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC  
Erbitux is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as “Ras” or when the Ras status is unknown.

Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials including Study 4 were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. [See Indications and Usage (1.2), Clinical Pharmacology (12.1), Clinical Studies (14.2)].

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)  
In Combination with FOLFIRI  
(…) The safety of a cetuximab product in combination with FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…)  
As Single-Agent  
The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, mCRC [see Warnings and Precautions (5.8)]. (See Table 5) (…)  

14 CLINICAL STUDIES  
14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)  
In Combination with FOLFIRI  
CRYSTLAL (NCT00154102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive either a cetuximab product in combination with FOLFIRI alone as first-line treatment. Stratification factors were Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 versus 2) and region (Western Europe versus Eastern Europe versus other). (…)  

In Combination with Irinotecan  
ERBITUX at the recommended dosage was administered in combination with irinotecan in 354 patients with EGFR expressing recurrent mCRC in Study CP02-9923 and BOND. (…)  

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<td>125084, 09/24/2021</td>
<td>Cetuximab (3)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>1 INDICATIONS AND USAGE</td>
<td>1.3 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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<td>020989, 12/08/2006</td>
<td>Cevimeline</td>
<td>Dental</td>
<td>CYP2D6</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
<td>2.1 Patient Selection</td>
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<td>006002, 10/24/2018</td>
<td>Chloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
<td>8.5 Geriatric Use</td>
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<td>011641, 02/01/2011</td>
<td>Chlorpropamide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>14 CLINICAL STUDIES</td>
<td>14.3 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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<td>009435, 11/02/2018</td>
<td>Chloroprocaine</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonlurea agents can lead to hemolytic anemia. Because DIABINESE belongs to the class of sulfonlurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonlurea alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.</td>
</tr>
</tbody>
</table>
| 009435, 11/02/2018                     | Chloroprocaine | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings | Methemoglobinemia. Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 205750, 10/22/2020                    | Cholic Acid | Inborn Errors of Metabolism | AMACR, AKR1D1, CYP7A1, CYP27A1, DHCR7, HSD3B2 (Bile Acid Synthesis Disorders) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Bile Acid Synthesis Disorders Due to Single Enzyme Defects
CHOLBAM is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).
1.3 Limitations of Use
The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.
2 DOSAGE AND ADMINISTRATION
2.1 Dosage Regimen for Bile Acid Synthesis Disorders Due to SEDs and PDs Including Zellweger Spectrum Disorders
The recommended dosage of CHOLBAM is 10 to 15 mg/kg administered orally once daily or in two divided doses, in pediatric patients and adults. (…)
2.2 Treatment Monitoring
(…) Assessment of serum or urinary bile acid levels using mass spectrometry is used in the diagnosis of bile acid synthesis disorders due to SEDs and PDs including Zellweger spectrum disorders. The utility of bile acid measurements in monitoring the clinical course of patients and in decisions regarding dose adjustment has not been demonstrated.
5 WARNINGS AND PRECAUTIONS
5.1 Exacerbation of Liver Impairment
In clinical trials, evidence of liver impairment was present before treatment with CHOLBAM in approximately 86% (44/51) of patients with bile acid synthesis disorders and in approximately 50% (14/28) of patients with PDs including Zellweger spectrum disorders. Five of the patients (3 SED and 2 PD) with liver impairment at baseline experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy following treatment. Five additional patients (2 SED and 3 PD) who did not have baseline cholestasis experienced exacerbation of their liver disease while on treatment. In patients with cirrhosis, cases of severe hepatotoxicity have also been observed following postmarket use of CHOLBAM. Exacerbation of liver impairment by CHOLBAM in these patients cannot be ruled out. Six patients with SEDs underwent liver transplant, including four patients diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency, and one with CYP7A1 deficiency. (…)
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Clinical safety experience with CHOLBAM consists of:
• Trial 1: a non-randomized, open-label, single-arm trial of 50 patients with bile acid synthesis disorders due to SEDs and 29 patients with PDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.
• Trial 2: an extension trial of 12 new patients (10 SED and 2 PD) along with 31 (21 SED and 10 PD) patients who rolled over from Trial 1. Safety data are available for 3 years and 11 months of treatment. (…)
Deaths
In Trial 1, among the 50 patients with SEDs, 5 patients aged 1 year or less died, which included three patients originally diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency and one with CYP7A1 deficiency. The cause of death was attributed to progression of underlying liver disease in every patient. Of 29 patients in Trial 1 with PDs including Zellweger spectrum disorders, 12 patients between the ages of 7 months and 2.5 years died. In the majority of these patients (8/12), the cause of death was attributed to progression of underlying liver disease or to a worsening of their primary illness. Two additional patients in Trial 1 (1 SED and 1 PD) died who had been off study medication for more than one year with the cause of death most likely being a progression of underlying liver disease. Of the patients who died with disease progression, laboratory testing showed abnormal serum transaminases, bilirubin, or cholestasis on liver biopsy suggesting worsening of their underlying cholestasis. In Trial 2, among the 31 patients with SED, two patients (1 new patient and 1 who rolled over from Trial 1) died. The cause of death in both cases was unrelated to their primary treatment or progression of their underlying liver disease. |

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<td>Oncology</td>
<td>TPMT</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Ototoxicity</td>
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<td></td>
<td>(…). Genetic factors (e.g., variants in the thiopurine S-methyltransferase (TPMT) gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.</td>
</tr>
<tr>
<td>020822, 01/11/2019</td>
<td>Citalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Warnings, Clinical Pharmacology</td>
<td>DOSAGE AND ADMINISTRATION</td>
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<tr>
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<td></td>
<td>Special Populations</td>
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<tr>
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<td>20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age, patients with hepatic impairment, and for CYP2C19 poor metabolizers or those patients taking cimetidine or another CYP2C19 inhibitor. (see WARNINGS)</td>
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<td></td>
<td>WARNINGS</td>
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<td>QT-Prolongation and Torsade de Pointes</td>
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<td>The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected.</td>
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<td>Citalopram (2)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>(…) CYP2C19 poor metabolizers – In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION). CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.</td>
</tr>
<tr>
<td>202067, 06/15/2018</td>
<td>Clobazam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam’s active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 [see Use in Specific Populations (8.6), Clinical Pharmacology (12.5)].</td>
</tr>
<tr>
<td>019906, 05/10/2019</td>
<td>Clomipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Drugs Metabolized by P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (…)</td>
</tr>
<tr>
<td>020839, 05/17/2019</td>
<td>Clopidogrel</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Boxed Warning, Warnings and Precautions, Clinical Pharmacology</td>
<td>BOXED WARNING WARNING Diminished antplatelet effect in patients with two loss-of-function alleles of the CYP2C19 gene The effectiveness of Plavix results from its antplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed “CYP2C19 poor metabolizers”). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.</td>
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| 019758, 02/23/2017                     | Clozapine   | Psychiatry        | CYP2D6     | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION

2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers

It may be necessary to reduce the CLOZARIL dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)].

8 USE IN SPECIFIC POPULATIONS

8.7 CYP2D6 Poor Metabolizers

Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted [see Dosage and Administration (2.7), Clinical Pharmacology (12.3)].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

CYP2D6 Poor Metabolizers

A subset (3%-10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.

| 206192, 10/28/2022                     | Cobimetinib | Oncology          | BRAF       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE

COTELLIC® is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Melanoma

Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with COTELLIC with vemurafenib. Information on FDA approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnositics.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

(…) The safety of COTELLIC was evaluated in Trial 1, a randomized (1:1), double blind, active-controlled trial in previously untreated patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma [see Clinical Studies (14)]. (…) 14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The safety and efficacy of cobimetinib was established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation assay. (…) The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review. A trend favoring the cobimetinib arm was observed in exploratory subgroup analyses of PFS, OS, and ORR in both BRAF V600E mutation subtypes (V600E or V600K) in the 81% of patients in this trial where BRAF V600 mutation type was determined.

14.2 Histiocytic Neoplasms

A single-center, single-arm trial (Trial 2) was conducted to evaluate the efficacy, safety, and tolerability of COTELLIC as a single agent in adult patients with histologically confirmed histiocytic neoplasms of any mutational status. Patients with documented BRAF V600E mutations were enrolled if they were unable to access a BRAF inhibitor or discontinued a BRAF inhibitor due to toxicity. Enrolled patients had multi-system disease, recurrent or refractory disease, or single-system disease that is unlikely to benefit from conventional therapies, based on best available evidence. The trial included 26 patients with histiocytic neoplasms including Langerhans Cell Histiocytosis (n=4), Rosai-Dorfman Disease (n=4), Erdheim-Chester Disease (n=13), Xanthogranuloma (n=2) and Mixed Histiocytosis (n=3). Patients with BRAF V600E mutant positive (n=6) and BRAF V600 Wild type (n=20) received COTELLIC. (…)

| 022402, 09/18/2018                     | Codeine     | Anesthesiology    | CYP2D6     | Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient | BOXED WARNING

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE, INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

* Therapeutic areas do not necessarily reflect the CDER review division.

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<td>Adverse Reactions, Clinical Studies</td>
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Counseling Information

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being a ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism [see Warnings and Precautions (5.4)]. Codeine Sulfate Tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. Avoid the use of Codeine Sulfate Tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. (…)

5 WARNINGS AND PRECAUTIONS

5.4 Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. (…)

Nursing Mothers

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Codeine Sulfate Tablets [see Use in Specific Populations (8.2)].

CYP2D6 Genetic Variability; Ultra-Rapid Metabolizers

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as "1*1/kN or "1*2/kN"). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)]. Therefore, individuals who are ultra-rapid metabolizers should not use Codeine Sulfate Tablets.

8 USE IN SPECIFIC POPULATIONS

8.2 Lactation

Risk Summary

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerous high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Codeine Sulfate Tablets and any potential adverse effects on the breastfed infant from Codeine Sulfate Tablets or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Codeine Sulfate Tablets in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received codeine (see Warnings and Precautions (5.4)). In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine. (…)

17 PATIENT COUNSELING INFORMATION

Ultra-Rapid Codeine Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Advise caregivers that Codeine Sulfate Tablets are contraindicated in all children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children 12 to 18 years of age receiving Codeine Sulfate Tablets to monitor for signs of respiratory depression [see Warnings and Precautions (5.4)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Sickle Cell Disease

The safety of ADAKVEO was evaluated in the SUSTAIN trial [see Clinical Studies (14.1)]. Eligible patients were diagnosed with sickle cell disease (any genotype including HbSS, HbSC, HbSbeta0-thalassemia, HbSbeta+ thalassemia, and others). (…)

14 CLINICAL STUDIES

The efficacy of ADAKVEO was evaluated in patients with sickle cell disease in SUSTAIN (NCT01893061), a 52-week, randomized, multicenter, placebo-controlled, double-blind study. A total of 198 patients with sickle cell disease, any genotype (HbSS, HbSC, HbSbeta0-thalassemia, HbSbeta+ thalassemia, and others), and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. (See Table 2) (…)

(…)

Patients with sickle cell disease who received ADAKVEO 5 mg/kg had a lower median annual rate of VOC compared to patients who received placebo (1.83 vs. 2.98) which was statistically significant (p = 0.016). Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use. (…)

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| 202570, 07/14/2022 | Crizotinib (1) | Oncology | ALK | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE

1.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)].

1.2 Relapsed or Refractory, Systemic ALK-Positive Anaplastic Large Cell Lymphoma

XALKORI is indicated for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.

1.3 Unresectable, Recurrent, or Refractory ALK-Positive Inflammatory Myofibroblastic Tumor

XALKORI is indicated for the treatment of adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Clinical Studies (14.1, 14.2)].

Information on FDA-approved tests for the detection of ALK and ROS1 rearrangements in NSCLC is available at http://www.fda.gov/companiondiagnostics.

2.2 Recommended Dosage for ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

See Table 1

2.4 Dosage Modifications for Adverse Reactions

**Recommended Dosage Reductions**

Adult Patients with ALK- or ROS1-positive Metastatic NSCLC or Adult Patients with ALK-positive IMT

The recommended dose reductions for adverse reactions are:

- First dose reduction: XALKORI 200 mg taken orally twice daily
- Second dose reduction: XALKORI 250 mg taken orally once daily
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily.

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

The recommended dose reductions for adverse reactions are provided in Table 3.

2.5 Dosage Modifications for Moderate and Severe Hepatic Impairment

Adult Patients with ALK- or ROS1-positive Metastatic NSCLC or with ALK-positive IMT

The recommended dose of XALKORI in patients with moderate hepatic impairment (any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN) is 200 mg orally twice daily.

The recommended dose of XALKORI in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is 250 mg orally once daily [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

The recommended dose of XALKORI in patients with severe hepatic impairment [any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN] is the second dose reduction based on BSA as shown in Table 3 [see Dosage and Administration (2.5), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

2.6 Dosage Modification for Severe Renal Impairment

Adult Patients with ALK- or ROS1-positive Metastatic NSCLC or with ALK-positive IMT

The recommended dose of XALKORI in patients with severe renal impairment (creatinine clearance (Clcr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation) is 250 mg orally once daily [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

The recommended dose of XALKORI in patients with severe renal impairment (Clcr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients is 250 mg orally once daily [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

2.7 Dosage Modification for Concomitant Use of Strong CYP3A Inhibitors

Adult Patients with ALK- or ROS1-positive metastatic NSCLC or with ALK-positive IMT

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to 250 mg orally once daily [see Drug Interactions (7.1)]. After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to the second dose reduction based on BSA as shown in Table 3 [see Dosage and Administration (2.4), Drug Interactions (7.1)]. After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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| 07/14/2022 | Crizotinib (2) | Oncology | ROS1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE 1.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)].

2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Clinical Studies (14.1, 14.2)]. Information on FDA-approved tests for the detection of ALK and ROS1 rearrangements in NSCLC is available at http://www.fda.gov/companiondiagnostics.

2.2 Recommended Dosage for ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer See Table 1.

2.4 Dosage Modifications for Adverse Reactions Recommended Dosage Reductions Adult Patients with ALK- or ROS1-Positive Metastatic NSCLC or Adult Patients with ALK-positive IMT The recommended dose reductions for adverse reactions are:
- First dose reduction: XALKORI 200 mg taken orally twice daily
- Second dose reduction: XALKORI 250 mg taken orally once daily
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily.

Pediatric and Young Adult Patients with ALK-positive ALC or Pediatric Patients with ALK-positive IMT The recommended dose reductions for adverse reactions are provided in Table 3.

2.5 Dosage Modifications for Moderate and Severe Hepatic Impairment Adult Patients with ALK or ROS1-Positive Metastatic NSCLC or with ALK-positive IMT |

| Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014; NCT01154140) | The efficacy of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 1). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit, prior to randomization. The major efficacy outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by independent radiology review (IRR) committee. Additional efficacy outcome measures included objective response rate (ORR) as assessed by IRR, DOR, and overall survival (OS). Patient-reported lung cancer symptoms were assessed at baseline and periodically during treatment. (See Table 12) (…)

Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007; NCT00932865) The efficacy of XALKORI as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum-based chemotherapy regimen, were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). The major efficacy outcome was PFS according to RECIST version 1.1 as assessed by IRR. Additional efficacy outcomes included ORR as assessed by IRR, DOR, and OS.

Patients were randomized to receive XALKORI 250 mg orally twice daily (n=173) or chemotherapy (n=174). Chemotherapy consisted of pemetrexed 500 mg/m² (if pemetrexed-naïve; n=99) or docetaxel 75 mg/m² (n=72) intravenously (IV) every 21 days. Patients in both treatment arms continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Randomization was stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization. (See Table 13) (…)

14.2 Relapsed or Refractory, Systemic ALK-Positive Anaplastic Large Cell Lymphoma The efficacy of XALKORI was evaluated in Study ADVL0912 (NCT00939770), a multicenter, single-arm, open-label study in patients 1 to ≤21 years of age that included 26 patients with relapsed or refractory, systemic ALK-positive ALCCL at least one systemic treatment. ALK positive status (confirmation of an ALK fusion) was determined locally by immunohistochemistry or fluorescence in situ hybridization. The study excluded patients with primary cutaneous ALCCL or central nervous system involvement by lymphoma. (See Table 18) (…)

14.3 Unresectable, Recurrent, or Refractory ALK-Positive Inflammatory Myofibroblastic Tumor Pediatric Patients with ALK-positive IMT Study ADVL0912 The efficacy of XALKORI was evaluated in Study ADVL0912 (NCT00939770), a multicenter, single-arm, open-label study in patients 1 to ≤21 years of age that included 14 pediatric patients with unresectable, recurrent, or refractory ALK-positive IMT. Patients were required to have an ALK fusion determined locally by immunohistochemistry or fluorescence in situ hybridization. Patients (n=12) received XALKORI 280 mg/m² twice daily until disease progression or unacceptable toxicity. Two patients received a lower dose. (see Table 19) Adult Patients with ALK-positive IMT Study A8081013 The efficacy of XALKORI was evaluated in Study A8081013 (NCT01121588), a multicenter, single-arm, open-label study that included 7 adult patients with unresectable, recurrent, or refractory ALK-positive IMT. ALK fusion was determined locally by immunohistochemistry or fluorescence in situ hybridization. Patients received XALKORI 250 mg twice daily. Two (29%) patients had at least one prior systemic treatment. The major efficacy outcome was objective response rate according to RECIST version 1.1 per investigator assessment. For the 7 patients with ALK-positive IMT, 5 experienced a response including 1 complete response. The DOR was 26 months for all 5 patients and ≥12 months for 2 patients. |

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The recommended dose of XALKORI in patients with moderate hepatic impairment (any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN) is 200 mg orally twice daily. The recommended dose of XALKORI in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is 250 mg orally once daily (see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)).

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

The recommended dose of XALKORI in patients with moderate hepatic impairment (any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN) is 200 mg orally twice daily. The recommended dose of XALKORI in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is 250 mg orally once daily (see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)).

2.7 Dosage Modification for Severe Renal Impairment

Adult Patients with ALK- or ROS1-positive Metastatic NSCLC or with ALK-positive IMT

The recommended dosage of XALKORI in patients with severe renal impairment (creatinine clearance (ClCr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation) is 250 mg orally once daily (see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

The recommended dosage of XALKORI in patients with severe renal impairment (ClCr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients is 250 mg orally once daily (see Table 3 [see Dosage and Administration (2.5), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

2.8 Dosage Modification for Concomitant Use of Strong CYP3A Inhibitors

Adolescents and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to 250 mg orally once daily (see Drug Interactions (7.1)). After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to the second dose reduction based on BSA as shown in Table 3 (see Dosage and Administration (2.4), Drug Interactions (7.1)). After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

ALK- or ROS1-Positive Metastatic NSCLC

The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3). (…)

ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001)

The safety profile of XALKORI from Study 3, which was evaluated in 50 patients with ROS1-positive metastatic NSCLC, was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC (n=1669). Vision disorders occurred in 92% of patients in Study 3: 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months. Study A8081013

The safety of XALKORI for adult patients with ALK-positive IMT was evaluated in Study A8081013 (see Clinical Studies (14.3)) that included 7 patients with IMT with median age of 38 years (range 23 to 73). The safety profile of this patient group was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive or ROS1-positive NSCLC. The most frequent adverse reactions (≥20%) were vision disorders, nausea, and edema.

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical studies of XALKORI in patients with ROS1-positive metastatic NSCLC did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

14 CLINICAL STUDIES

14.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

Previously Untreated ALK-Positive Metastatic NSCLC - Study 7 (PROFILE 1014; NCT01154140)

The efficacy of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 1). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit, prior to randomization. The major efficacy outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by independent radiology review (IRR) committee. Additional efficacy outcome measures included objective response rate (ORR) as assessed by IRR, DOR, and overall survival (OS). Patient-reported lung cancer symptoms were assessed at baseline and periodically during treatment. (…)

ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001; NCT00585195)

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<td>202806, 05/26/2023</td>
<td>Dabrafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older, ECOG performance status of 0, 1, or 2, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRR and investigator, with imaging performed every 8 weeks for the first 60 weeks. Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (98%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (80%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (98%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. Efficacy results are summarized in Table 17.</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 12/2023

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- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Clinical Studies (14.7)]. An FDA-approved test for the detection of BRAF V600E mutation in LGG is not currently available.

5 WARNINGS AND PRECAUTIONS

5.2 Tumor Promotion in BRAF Wild-Type Melanoma

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of TAFINLAR as a single agent or in combination with trametinib [see Indications and Usage (1.6), Dosage and Administration (2.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the Warnings and Precautions sections reflect exposure to TAFINLAR administered as a single agent in 586 patients with various solid tumors and exposure to TAFINLAR administered with trametinib in 559 patients with melanoma and 93 patients with NSCLC. The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600E mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 600 mg).

Metastatic or Unresectable BRAF V600 Mutation Positive Melanoma

TAFINLAR as a Single Agent

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of the BREAK-3 study [see Clinical Studies (14.1)]. This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m2 intravenously every 3 weeks (n = 63). TAFINLAR Administered with Trametinib

The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma who received TAFINLAR in two trials, Trial 2 (n = 209) a multicenter, double-blind, randomized (1:1), active controlled trial and Trial 3 (n = 350) a multicenter, open-label, randomized (1:1), active controlled trial. (…)

Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The safety of TAFINLAR when administered with trametinib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study [see Clinical Studies (14.3)]. (…)

Metastatic, BRAF V600E-Mutation Positive, Non-Small Cell Lung Cancer (NSCLC)

The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928). (…)

Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC)

The safety of TAFINLAR when administered with trametinib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). (…)

Advanced BRAF V600E-Mutation Positive Tumors

Study BRF117019

The safety of TAFINLAR when administered with trametinib was evaluated in a multi-cohort, multi-center, non-randomized, open-label study in adult patients with a BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumor cohorts, and 65 in other malignancies [see Clinical Studies (14.5, 14.6)]. Patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. (…)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors and LGG

The safety and effectiveness of TAFINLAR in combination with trametinib have been established in pediatric patients 6 years of age and older with unresectable or metastatic solid tumors bearing a BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; and patients 1 year of age and older with LGG with BRAF V600E mutation who require systemic therapy. Use of TAFINLAR in combination with trametinib for these indications is supported by evidence from studies X2101 and G2201 that enrolled 171 patients (1 to < 18 years) with BRAF V600E mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (23%) patients were 2 to < 6 years of age, 54 (32%) patients were 6 to < 12 years of age, and 74 (43%) patients were 12 to < 18 years of age [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.6, 14.7)].

The safety and effectiveness of TAFINLAR in combination with trametinib have not been established in pediatric patients younger than 1 year old with LGG with BRAF V600E mutation, and in patients < 6 years old with unresectable or metastatic solid tumors with BRAF V600E mutation.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

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The potential effect of TAFINLAR on QT prolongation was assessed in a dedicated multiple-dose study in 32 patients with BRAF V600 mutation-positive tumors. No large changes in the mean QT interval (i.e., >20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage).

14 CLINICAL STUDIES

14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent

BREAK-3

In the BREAK-3 study (NCT01227889), the safety and efficacy of TAFINLAR as a single agent were demonstrated in an international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. (…)

(…)

All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were tested retrospectively, using an FDA-approved companion diagnostic test. THxID™-BRAF assay. (…)

(…)

In supportive analyses based on irRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis.

BREAK-MB

Study The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multicenter trial (the BREAK-MB study; NCT01266987). (…)

14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR Administered with Trametinib

COMBI-d Study and COMBI-v Study

The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908).

The COMBI-d study compared TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or TAFINLAR 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal [ULN] vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

The COMBI-v study compared TAFINLAR and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal [ULN] vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1. (…)

(…)

All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations. (…)

In the COMBI-v study, 704 patients were randomized to TAFINLAR plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91 years), 96% were White, and 55% were male, 6% percent of patients had Stage IIIC, 61% had M1c disease, 67% had a normal LDH, 70% had ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases. (See Table 12 and Figures 2, 3)

COMBI-MB Study

(…)

The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84 years), 58% were male, 100% were white, 8% were from the United States, 65% had a normal LDH value at baseline, and 97% had an ECOG performance status of 0 or 1. Intracranial metastases were asymptomatic in 87% and symptomatic in 13% of patients, 22% received prior local therapy for brain metastases, and 87% also had extracranial metastases. (…)

14.3 Adjunct Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

COMBI-AD (NCT 01682083) was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations as detected by the THxID™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomly (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or two placebos for up to 1 year. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable in-transit metastases, distant metastatic disease, or prior systemic anticancer intervention, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (Ila, Iib, or Iic). (…)

(…)

In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range 18-89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage Ila (18%), Stage Iib (41%), Stage Iiec (40%), stage unknown (1%), BRAF V600E mutation (91%), BRAF V600K mutation (5%), macroscopic lymph nodes (65%), and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 14) (…)

14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

In Study BRF113928 (NCT01336634), the safety and efficacy of TAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC; no prior exposure to BRAF or MEK inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). (…)

(…)

In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 15. (See Table 15)
Table of Pharmacogenomic Biomarkers in Drug Labeling

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14.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer (ATC)
The safety and efficacy of TAFINLAR administered with trametinib was evaluated in Study BRF117019 (NCT02034110), an activity estimating, nine-cohort, multi-center, non-comparative, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication; who received prior treatment with BRAF or MEK inhibitors; with symptomatic or untreated CNS metastases; or who had airway obstruction. (…)

14.6 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors
The safety and efficacy of TAFINLAR in combination with trametinib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT2122X101, and supported by results in COMB1b, COMB1-v (see Clinical Studies [14.2]), and BRF113928 (see Clinical Studies [14.4]). In adult studies, patients received TAFINLAR 150 mg twice daily and trametinib 2 mg once daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR).

202806, 05/26/2023
Dabrafenib (2) Oncology G6PD

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<td>Oncology</td>
<td>(RAS)</td>
<td>Dosage and Administration, Warnings and Precautions</td>
<td>2 DOSAGE AND ADMINISTRATION 2.3 Dosage Modifications for Adverse Reactions Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies. (See Table 2)</td>
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<td>206843, 11/09/2017</td>
<td>Daclatasvir</td>
<td>Infectious Diseases</td>
<td>(\text{IFNL3 (IL28B)})</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Clinical Trials in HCV Genotype 3 (ALLY-3) (…) The 152 treated subjects in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the subjects were male; 90% were white, and 4% were black. Most subjects (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype. SVR12 and outcomes in subjects without SVR12 in ALLY-3 are shown by patient population in Table 13. SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B allele status, or baseline HCV RNA level. For SVR outcomes related to baseline NSSA amino acid polymorphisms, see Microbiology (12.4). (…) 14.3 Clinical Trials in HCV/HIV Coinfected Subjects (ALLY-2) (…) Most subjects (80%) had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 16% of the subjects had compensated cirrhosis, and 73% had IL28B rs12979860 non-CC genotype. (…) (…) SVR12 rates were comparable regardless of antiretroviral therapy, HCV treatment history, age, race, gender, IL28B allele status, HCV genotype 1 subtype, or baseline HCV RNA level. For SVR outcomes related to baseline NSSA amino acid polymorphisms, see Microbiology (12.4) (…) 14.4 Clinical Trials in Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Recurrence after Liver Transplantation (ALLY-1) (…) Fifty-eight percent of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 10% had genotype 3, 4% had genotype 4, and 1% had genotype 6; 77% had IL28B rs12979860 non-CC genotype. (…) (…) SVR12 rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level. For SVR12 outcomes related to baseline NSSA amino acid polymorphisms, see Microbiology (12.4) (…)</td>
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<tr>
<td>211288, 09/27/2018</td>
<td>Dacomitinib</td>
<td>Oncology</td>
<td>(\text{EGFR})</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE VIZIMPRO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test [see Dosage and Administration (2.1)]. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the first-line treatment of metastatic NSCLC with VIZIMPRO based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (…) The data in the Warnings and Precautions section reflect exposure to VIZIMPRO in 394 patients with first-line or previously treated NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test [see Clinical Studies (14)]. 8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use Of the total number of patients (N=394) in five clinical studies with EGFR mutation-positive NSCLC who received VIZIMPRO at a dose of 45 mg once daily in a randomized, active-controlled trial [ARCHER 1050 (N=227), Study A7471008 (N=38), Study A7471011 (N=83), and Study A7471028 (N=16)] and one single-arm trial [Study A7471017 (N=30)]. The median duration of exposure to VIZIMPRO was 10.8 months (range 0.07-68) [see Warnings and Precautions (5)]. The data described below reflect exposure to VIZIMPRO in 227 patients with EGFR mutation-positive, metastatic NSCLC enrolled in a randomized, active-controlled trial (ARCHER 1050); 224 patients received gefitinib 250 mg orally once daily in the active control arm [see Clinical Studies (14)].</td>
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| **021794, 05/18/2018** | Dapsone (1) | Dermatology | G6PD | Warnings and Precautions, Use in Specific Populations, Patient Counseling Information | **5 WARNINGS AND PRECAUTIONS**

### 5.2 Hematologic Effects

Oral dapson treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry. Some subjects with G6PD deficiency using ACZONE® Gel developed laboratory changes suggestive of hemolysis. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel, 5%, including patients who were G6PD deficient. Discontinue ACZONE® Gel, 5%, if signs and symptoms suggestive of hemolytic anemia occur. Avoid use of ACZONE® Gel, 5% in patients who are taking oral dapson or antimarial medications because of the potential for hemolytic reactions. Combination of ACZONE® Gel, 5%, with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.2 Lactation Risk

Summary: There is no information regarding the presence of topical dapson in breastmilk, the effects on the breastfed infant, or the effects on milk production. Orally administered dapson appears in human milk and could result in hemolytic anemia and hyperbilirubinemia especially in infants with G6PD deficiency. Systemic absorption of dapson following topical application is minimal relative to oral dapson administration; however, it is known that dapson is present in human milk following administration of oral dapson.

#### 8.6 G6PD Deficiency

ACZONE® Gel, 5% and vehicle were evaluated in a randomized, double-blind, cross-over design clinical study of 64 patients with G6PD deficiency and acne vulgaris. Subjects were Black (88%), Asian (6%), Hispanic (2%) or of other racial origin (5%). Blood samples were taken at Baseline, Week 2, and Week 12 during both vehicle and ACZONE® Gel, 5% treatment periods. There were 56 out of 64 subjects who had a Week 2 blood draw and applied at least 50% of treatment applications. Table 3 contains results from testing of relevant hematology parameters for these two treatment periods. ACZONE® Gel was associated with a 0.32 g/dL drop in hemoglobin after two weeks of treatment, but hemoglobin levels generally returned to baseline levels at Week 12. (See Table 3) There were no changes from baseline in hematocrit in subjects who received vehicle treatment at either the 2-week or 12-week time point. The proportion of subjects who experienced decreases in hemoglobin ≥1 g/dL was similar between ACZONE® Gel, 5% and vehicle treatment (8 of 58 subjects vs 7 of 56 subjects, respectively) compared to subjects with at least one on-treatment hemoglobin assessment. Subgroups based on gender, race, or G6PD enzyme activity did not display any differences in laboratory results from the overall study group. There was no evidence of clinically significant hemolytic anemia in this study. Some of these subjects developed laboratory changes suggestive of hemolysis.

### 17 PATIENT COUNSELING INFORMATION

**Advisement:** The patient to read the FDA-approved patient labeling (Patient Information). Hematological Effects

- Inform patients that methemoglobinemia can occur with topical dapson treatment. Advise patients to seek immediate medical attention if they develop cyanosis (see Warnings and Precautions (5.1)).
- Inform patients who have G6PD deficiency that hemolytic anemia may occur with topical dapson treatment. Advise patients to seek medical attention if they develop signs and symptoms suggestive of hemolytic anemia (see Warnings and Precautions (5.2)).

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Methemoglobinemia

Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE® Gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of ACZONE® Gel, 5% in those patients with congenital or idiopathic methemoglobinemia. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in, e.g., buccal mucous membranes, lips and nail beds. Advise patients to discontinue ACZONE® Gel, 5% and seek immediate medical attention in the event of cyanosis.

Dapsone can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents.

### 6 ADVERSE REACTIONS

#### 6.3 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use of topical dapson: methemoglobinemia, rash (including erythematous rash, application site rash) and swelling of face (including lip swelling, eye swelling).

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<th>Labeling Sections</th>
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<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>Dasatinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>Hispanic or Latino: 21% had a body mass index of at least 30 kg per m²; 21% of patients were enrolled in US sites; 83% had IL28B (rs12979860) nonCC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per ml. (…)</td>
</tr>
</tbody>
</table>

14.5 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection and Compensated Cirrhosis

(…) Treated subjects had a median age of 58 years (range: 21 to 71); 70% of the subjects were male; 95% were White; 3% were Black/African American; 12% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m²; 43% of patients were enrolled in US sites; 82% had IL28B (rs12979860) non-CC genotype; 89% had baseline HCV RNA levels of at least 800,000 IU per ml; 69% had HCV GT1a infection; 42% were treatment-naïve, 36% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 14% were prior pegIFN/RBV relapsers; 15% had platelet counts of less than 90 x 10⁹ per L; 50% had albumin less than 4.0 mg per dl. (…) |

14.6 Clinical Trial in Subjects with HCV/HIV-1 Co-infection (TURQUOISE-I)

(…) Treated subjects had a median age of 51 years (range: 31 to 69); 24% of subjects were black; 81% of subjects had IL28B (rs12979860) non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects had HCV genotype 1a infection. (…) |

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5.1 Myelosuppression
Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML. In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated. (…)

In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery. (…)

5.2 Bleeding-Related Events
In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction in vitro. In all CML or Ph+ ALL clinical studies, 2 grade 3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. Grade 3 or greater gastrointestinal hemorrhage, including fatalities, occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of grade 3 hemorrhage occurred in 2% of patients. Most bleeding events in clinical studies were associated with severe thrombocytopenia. Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

5.3 Fluid Retention
(…) In patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural effusion reported in 7% of patients. (…)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…) The data described below reflect exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and in 2398 patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2712 SPRYCEL-treated patients was 19.2 months (range 0–93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1618 patients with chronic phase CML was 29 months (range 0–92.9 months). The median duration of therapy in 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months). (…)

(…) In the randomized trial in patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 36%. Among the 1618 SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation were reported in 326 (20.3%) patients; among the 1094 SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, drug-related adverse events leading to discontinuation were reported in 191 (17.5%) patients. (…)

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults
A total of 1035 patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. (…)

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients
The safety of SPRYCEL administered continuously in combination with multigagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL. (See Clinical Studies (14.4) and Pediatric Patients (14.3)). The median duration of therapy was 24 months (range 2 to 27 months). (…)

6.2 Additional Pooled Data From Clinical Trials
The following additional adverse reactions were reported in patients in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These events are included on the basis of clinical relevance.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
Ph+ CML in Chronic Phase
The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML (see Clinical Studies (14.3)). There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of patients (see Warnings and Precautions (14.10)).

Ph+ ALL
The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients over one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported. The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects (see Adverse Reactions (6.1) and Clinical Studies (14.3, 14.4)).

Monitor bone growth and development in pediatric patients (see Warnings and Precautions (14.10)).

Pediatric Patients with Difficulty Swallowing Tablets
Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. (…)

14 CLINICAL STUDIES

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<td>PRECAUTIONS</td>
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<td>Denileukin Diftitox</td>
<td>Oncology</td>
<td>(CD25 antigen)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>11/09/2018</td>
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<td>Desmopressin</td>
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<td>1 INDICATIONS AND USAGE</td>
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| 02/0118, 11/01/2022 | Desflurane | Anesthesiology | CACNA1S, RYR1 (Genetic Susceptibility to Malignant Hyperthermia) | 2.1 Pretreatment Testing and On-Treatment Monitoring: Hemophilia A. Prior to treatment with DDAVP injection, verify that factor VIII coagulant activity levels are >5% and exclude the presence of factor VIII autoantibodies. Also assess serum sodium and sPTT prior to treatment. In certain clinical situations, it may be justified to try DDAVP in patients with factor VIII levels between 2% to 5%; however, these patients should be carefully monitored. von Willebrand’s Disease (Type I). Prior to treatment with DDAVP injection, verify that factor VIII coagulant activity levels are >5% and exclude severe von Willebrand’s disease (Type I) and presence of abnormal molecular form of factor VIII antigen. During treatment with DDAVP injection, assess serum sodium, bleeding time, factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand antigen to ensure that adequate levels are being achieved. For All Patients Receiving Repeated Doses: Restrict free water intake and monitor for hyponatremia. Ensure that serum sodium is normal prior to initiating or resuming treatment with DDAVP injection. 2.2 Recommended Dosage: Hemophilia A and von Willebrand’s Disease (Type I). The recommended dosage is 0.3 mcg/kg actual body weight (to a maximum of 20 mcg) administered by intravenous infusion over 15 minutes to 30 minutes. If used preoperatively, administer 30 minutes prior to the procedure. If used to reduce spontaneous or traumatic bleeding, doses may be repeated after 8 hours to 12 hours and once daily thereafter, if needed, based upon clinical condition and von Willebrand factor and factor VIII levels. The necessity for repeat administration of DDAVP or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. Tachyphylaxis (lessening of response) with repeated administration (i.e., given more frequently than every 48 hours) may occur. The initial response is reproducible if DDAVP is administered every 2 to 3 days. 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics: The response to DDAVP of factor VIII activity and plasminogen activator is dose-related, with maximal plasma levels of 300 to 400 percent change from baseline obtained after infusion of 0.4 mcg/kg. The increase of factor VIII is rapid and evident within 30 minutes, reaching a maximum at a point ranging from 90 minutes to two hours. The duration of the hemostatic effect depends on the half-life for VIII:C which is about 8-12 hours. The percentage increase of factor VIII levels in patients with mild hemophilia A and von Willebrand’s disease was not significantly different from that observed in normal healthy individuals when treated with 0.3 mcg/kg of DDAVP infused over 10 minutes. The use of DDAVP Injection in patients with central diabetes insipidus reduces urinary output, increases urine osmolality, and decreases plasma osmolality. 4 CONTRAINdicATIONS: The use of SUPRANE is contraindicated in the following conditions:  
- Known or suspected genetic susceptibility to malignant hyperthermia.  
- Malignant Hyperthermia: 5.1 Malignant Hyperthermia: In susceptible individuals, volatile anesthetic agents, including desflurane, may trigger malignant hyperthermia, a skeletal muscle hypermetabolic state leading to high oxygen demand. Fatal outcomes of malignant hyperthermia have been reported. The risk of developing malignant hyperthermia increases with the concomitant administration of succinylcholine and volatile anesthetic agents. SUPRANE can induce malignant hyperthermia in patients with known or suspected susceptibility based on genetic factors or family history, including those with certain inherited ryanodine receptor (RYR1) or dihydropyridine receptor (CACNA1S) variants.  [see Contraindications (4), Clinical Pharmacology (12.5)] (…). 12.3 Pharmacokinetics: RYR1 and CACNA1S are polymorphic genes and multiple pathogenic variants have been associated with malignant hyperthermia susceptibility (MHS) in patients sensitive to volatile anesthetic agents, including SUPRANE. Case reports as well as ex vivo studies have identified multiple variants in RYR1 and CACNA1S associated with MHS. Variant pathogenicity should be assessed based on prior clinical experience, functional studies, prevalence information, or other evidence [see Contraindications (4), Warnings and Precautions (5.1)]. |
| 02/1992, 02/06/2018 | Desvenlafaxine | Psychiatry | CYP2D6 | 2 DOSAGE AND ADMINISTRATION: 2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers: In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Use in Specific Populations (8.7)]. |
| 206082, 05/04/2022 | Deutetrabenzine | Neurology | CYP2D6 | 8 USE IN SPECIFIC POPULATIONS: 8.7 Poor CYP2D6 Metabolizers: |

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<td>Dextansoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>Although the pharmacokinetics of deutetranabenzine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme, it is likely that the exposure to o-HTBZ and β-HTBZ would be increased similarly to taking a strong CYP2D6 inhibitor (approximately 3-fold). In patients who are CYP2D6 poor metabolizers, the daily dose of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].</td>
</tr>
<tr>
<td>021879, 06/11/2019</td>
<td>Dextromethorphan and Quinidine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Concomitant use of CYP2D6 Substrates The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 [see Drug Interactions (7.5)].</td>
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<td>Diazepam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Excretion NUEDEXTA is a combination product containing dextromethorphan and quinidine. Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. After dextromethorphan 30mg/quinidine 30mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours. (...)</td>
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<tr>
<td>125516, 03/01/2017</td>
<td>Dinutuximab</td>
<td>Oncology</td>
<td>MYCN</td>
<td>Clinical Studies</td>
<td>(...) Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. (...)</td>
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</table>
| 022234, 10/11/2019                     | Docetaxel | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 12 CLINICAL STUDIES 14.2 Adjuvant Treatment of Breast Cancer (...) Docetaxel was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC. (See Table 14) (...)
| 204790, 09/06/2018                     | Dolutegravir | Infectious Diseases | UGT1A1 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). (...)
| 020690, 12/18/2018                     | Donepezil | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoforms 2D6 and 3A4 and undergoes glucuronidation. Following administration of 14C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (46%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. Excretion of plasma radioactivity of CYP2D6 genotype in Alzheimer’s patients showed differences in clearance values among CYP2D6 genotype subgroups. When compared to the extensive metabolizers, poor metabolizers had a 31.5% slower clearance and ultra-rapid metabolizers had a 24% faster clearance. |
| 761114, 07/31/2023                     | Dostarlimab-gxly | Oncology | Microsatellite Instability, Mismatch Repair | Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE 1.1 Endometrial Cancer JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H) [see Dosage and Administration (2.1)]. JEMPERLI, as a single agent, is indicated for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation [see Dosage and Administration (2.1)]. 1.2 Mismatch Repair Deficient Recurrent or Advanced Solid Tumors JEMPERLI, as a single agent, is indicated for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options [see Dosage and Administration (2.1)]. This *

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**Table 4** summarizes the laboratory abnormalities in patients with primary advanced or recurrent dMMR/MSI-H EC receiving JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

**Table 3** summarizes the adverse reactions that occurred in ≥10% of patients with primary advanced or recurrent dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

The safety of JEMPERLI in patients with primary advanced or recurrent dMMR/MSI-H EC was evaluated in RUBY [see Clinical Studies (14.1)]. Patients received JEMPERLI 500 mg (n = 52) or placebo (n = 65) in combination with carboplatin and paclitaxel every 3 weeks for 6 doses followed by JEMPERLI 1,000 mg or placebo every 6 weeks until disease progression or unacceptable toxicity. Among the 52 patients, 56% were exposed for >1 year and 31% were exposed for >2 years.

The safety of JEMPERLI in patients with advanced or recurrent dMMR/MSI-H Primary Advanced or Recurrent EC: JEMPERLI In Combination with Carboplatin and Paclitaxel

The safety of JEMPERLI in patients with primary advanced or recurrent dMMR/MSI-H EC was evaluated in RUBY [see Clinical Studies (14.1)]. Patients received JEMPERLI 500 mg (n = 52) or placebo (n = 65) in combination with carboplatin and paclitaxel every 3 weeks for 6 doses followed by JEMPERLI 1,000 mg or placebo every 6 weeks until disease progression or unacceptable toxicity. Among the 52 patients, 56% were exposed for >1 year and 31% were exposed for >2 years.

The safety of JEMPERLI in patients with advanced or recurrent dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

Clinically relevant adverse reactions in <10% of patients with primary advanced or recurrent dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel included:

- Nervous System Disorders: Encephalopathy.
- Metabolism and Nutrition Disorders: Type 1 diabetes mellitus.
- Gastrointestinal Disorders: Colitis, pancreatitis.
- Eye Disorders: Keratitis.
- Endocrine Disorders: Hyperthyroidism, thyroiditis.
- Gastrointestinal Disorders: Colitis, pancreatitis.
- Metabolism and Nutrition Disorders: Type 1 diabetes mellitus.
- Nervous System Disorders: Encephalopathy.

The safety of JEMPERLI in patients with advanced or recurrent dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

The safety of JEMPERLI was evaluated in GARNET in 150 patients with advanced or recurrent dMMR/MSI-H EC who received at least 1 dose of JEMPERLI [see Clinical Studies (14.1), (See Tables 5 and 6) (…)].

The safety of JEMPERLI was evaluated in GARNET in 150 patients with advanced or recurrent dMMR/MSI-H EC who received at least 1 dose of JEMPERLI [see Clinical Studies (14.1), (See Tables 5 and 6) (…)].

The safety of JEMPERLI was investigated in 267 patients with recurrent or advanced dMMR solid tumors enrolled in GARNET [see Clinical Studies (14.2), (See Tables 7 and 8) (…)].

**14 CLINICAL STUDIES**

**14.1 Endometrial Cancer**

The efficacy of JEMPERLI in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, was evaluated in RUBY (NCT02981796), a randomized, multicenter, double-blind, placebo-controlled trial. Efficacy was assessed in a pre-specified subgroup of 122 patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer.

The identification of dMMR/MSI-H tumor status was prospectively determined based on local testing assays (IHC, PCR or NGS), or central testing (IHC) using the VENTANA MMR Dx Panel when no local result was available.

Randomization was stratified by MMR/MSI status, prior external pelvic radiotherapy, and disease status (recurrent, primary Stage III, or primary Stage IV).

Treatment with JEMPERLI continued until disease progression, unacceptable toxicity, or a maximum of 3 years. Administration of JEMPERLI was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.

Assessment of tumor status was performed every 6 weeks through Week 25, every 9 weeks through Week 52 and every 12 weeks thereafter. In the dMMR/MSI-H subgroup, the major efficacy outcome was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v 1.1). (See Table 9 and Figure 1)

As a Single Agent for the Treatment of dMMPERLI Recurrent or Advanced Endometrial Cancer

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This indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**

**Combination Therapy**

For use of JEMPERLI in combination with carboplatin and paclitaxel, select patients for treatment with JEMPERLI based on dMMR/MSI-H status in tumor specimens [see Clinical Studies (14.1)].

**Single Agent**

Select patients for treatment with JEMPERLI as a single agent based on the presence of dMMR in tumor specimens:

- recurrent or advanced endometrial cancer [see Clinical Studies (14.1)].
- recurrent or advanced solid tumors [see Clinical Studies (14.2)], Information on FDA-approved tests for the detection of dMMR status is available at [https://www.fda.gov/companiondiagnostics](https://www.fda.gov/companiondiagnostics).

- An FDA-approved test for the detection of MSI-H is not currently available [see Clinical Studies (14.1)].

Because the effect of prior chemotherapy on test results for dMMR in patients with high-grade gliomas is unclear, it is recommended to test for this marker in the primary tumor specimen obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

**2.2 Recommended Dosage**

The recommended dosage for JEMPERLI is presented in Table 1.

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**6 ADVERSE REACTIONS**

**Mismatch Repair Deficient (dMMR) or Microsatellite Instability-High (MSI-H) Primary Advanced or Recurrent EC: JEMPERLI In Combination with Carboplatin and Paclitaxel**

The safety of JEMPERLI in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, was evaluated in RUBY (NCT02981796), a randomized, multicenter, double-blind, placebo-controlled trial. Efficacy was assessed in a pre-specified subgroup of 122 patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer.

The identification of dMMR/MSI-H tumor status was prospectively determined based on local testing assays (IHC, PCR or NGS), or central testing (IHC) using the VENTANA MMR Dx Panel when no local result was available.

Randomization was stratified by MMR/MSI status, prior external pelvic radiotherapy, and disease status (recurrent, primary Stage III, or primary Stage IV).

Treatment with JEMPERLI continued until disease progression, unacceptable toxicity, or a maximum of 3 years. Administration of JEMPERLI was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.

Assessment of tumor status was performed every 6 weeks through Week 25, every 9 weeks through Week 52 and every 12 weeks thereafter. In the dMMR/MSI-H subgroup, the major efficacy outcome was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v 1.1). (See Table 9 and Figure 1)

As a Single Agent for the Treatment of dMMPERLI Recurrent or Advanced Endometrial Cancer
**Table of Pharmacogenomic Biomarkers in Drug Labeling**

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<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker‡</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</thead>
<tbody>
<tr>
<td><strong>022036, 03/17/2010</strong></td>
<td>Doxepin (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>The efficacy of JEMPERLI as a single agent was evaluated in the GARNET trial (NCT02715284), a multicenter, multicohort, open-label trial conducted in patients with advanced solid tumors. The efficacy population consisted of a cohort of 141 patients with dMMR recurrent or advanced EC who had progressed on or after treatment with a platinum-containing regimen. Approximately 43% of patients had received prior platinum-based chemotherapy and had no satisfactory alternative treatment options. Patients with dMMR endometrial cancer must have progressed on or after treatment with a platinum-containing regimen. Patients with dMMR colorectal cancer must have progressed after or been intolerant to a fluoropyrimidine, oxaliplatin, and irinotecan. At time of trial entry, 97.2% of patients (103/105) with non-endometrial dMMR solid tumors had Stage IV disease, and 68.0% (70/103) of patients with dMMR endometrial tumors had FIGO Stage IV disease. Evaluate the results are presented in Tables 11 and 12.</td>
</tr>
<tr>
<td><strong>022036, 03/17/2010</strong></td>
<td>Doxepin (2)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
<tr>
<td><strong>205525, 09/14/2018</strong></td>
<td>Dronabinol</td>
<td>Gastroenterology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>Published data indicate a 2- to 3-fold higher dronabinol exposure in individuals carrying genetic variants associated with diminished CYP2C9 function.</td>
</tr>
<tr>
<td><strong>021676, 08/09/2017</strong></td>
<td>Drospirenone and Ethinyl Estradiol</td>
<td>Gynecology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>Effects of Combined Oral Contraceptives on Other Drugs (…) In the study with 24 postmenopausal women [including 12 women with homozgous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. (…)</td>
</tr>
<tr>
<td><strong>021427, 12/19/2017</strong></td>
<td>Duloxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>Duloxetine plasma concentrations increased approximately 2-fold when administered with a potent CYP1A2 inhibitor compared to when administered alone.</td>
</tr>
<tr>
<td><strong>761088, 11/10/2022</strong></td>
<td>Durvalumab (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Clinical Studies</td>
<td>Indications and Usage: 1.1 Non-Small Cell Lung Cancer: IMFINZI is indicated for the treatment of adult patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.</td>
</tr>
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<th>Labeling Sections</th>
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</table>
| 76109, 11/10/2022                      | Durvalumab (2) | Oncology | EGFR | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Non-Small Cell Lung Cancer
- IMFINZI is indicated for the treatment of adult patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- IMFINZI, in combination with tremelimumab-actl and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. |
| 76109, 11/10/2022                      | Durvalumab (3) | Oncology | CD274 (PD-L1) | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Specific Populations
There were no clinically significant differences in the pharmacokinetics of durvalumab based on body weight (31 to 175 kg), age (18 to 96 years), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or Native American), albumin levels (4 to 57 g/L), lactate dehydrogenase levels (18 to 15,800 U/L), soluble PD-L1 (67 to 3,470 pg/mL), tumor type (NSCLC, SCLC, BTC and HCC), mild or moderate renal impairment (CLcr 30 to 89 mL/min), and mild or moderate hepatic impairment (bilirubin ≥ 3x ULN and any AST). The effect of severe renal impairment (CLcr 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3x ULN and any AST) on the pharmacokinetics of durvalumab is unknown. (…) |
| 211155, 09/26/2019                     | Duvelisib | Oncology | Chromosome 17p | Clinical Studies | 14 CLINICAL STUDIES
14.1 Efficacy in Relapsed or Refractory CLL/SLL Study 1
(…) In this subset (95 randomized to COPIKTRA, 101 to ofatumumab), the median patient age was 69 years (range: 40 to 90 years), 59% were male, and 88% had an ECOG performance status of 0 or 1. Forty-six percent received 2 prior lines of therapy, and 54% received 3 or more prior lines. At baseline, 52% of patients had at least one tumor ≥ 5 cm, and 22% of patients had a documented 17p deletion. (…) |
| 125166, 06/27/2019                     | Eculizumab (1) | Neurology | ACHR | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.3 Generalized Myasthenia Gravis (gMG)
Soliris is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive. |
| 125166, 06/27/2019                     | Eculizumab (2) | Neurology | AQP4 | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)
Soliris is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. |

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<tr>
<td>020972, 10/10/2017</td>
<td>Efavirenz</td>
<td>Infectious Diseases</td>
<td>CYP2B6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Cardiac Electrophysiology The effect of STUDYA on the QTc interval was evaluated in an open-label, positive and placebo-controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/<em>1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6</em>6/*6 genotype following the administration of 600 mg daily dose for 14 days [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>761195, 12/17/2021</td>
<td>Efgartigimod alfa-fcab</td>
<td>Neurology</td>
<td>ACHR</td>
<td>Indications and Usage, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE VYVGART is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (ACHR) antibody positive. 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics AChR-Ab positive patients. A statistically significant difference favoring VYVGART was observed in the QMG responder rate during the first treatment cycle (63.1% in the VYVGART-treated group vs 14.1% in the placebo-treated group (p &lt;0.0001)]. (See Table 2, Figures 1 and 2)</td>
</tr>
<tr>
<td>215500, 12/13/2023</td>
<td>Eflornithine</td>
<td>Oncology</td>
<td>MYCN</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS Study 3b (…) The median age of patients who received IWILFIN was 4 years (range: 1 to 17); 59% male; 85% White, 7% Black, 1% Asian, 8% Hispanic or Latino; 87% had International Neuroblastoma Staging System Stage 4 disease; 47% had neuroblastoma with known MYCN-amplification. (…)</td>
</tr>
<tr>
<td>217639, 01/27/2023</td>
<td>Elacestrant (1)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE ORSERDU is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ER1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for treatment of ER-positive, HER2-negative advanced or metastatic breast cancer with ORSERDU based on the presence of ESR1 mutation(s) in plasma specimen using an FDA-approved test [see Indications and Usage (1) and Clinical Studies (14)]. Information on FDA-approved tests for detection of ESR1 mutations in breast cancer is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 6 ADVERSE REACTIONS</td>
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<td>217639, 01/27/2023</td>
<td>Elacestrant (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>The safety of ORSERDU was evaluated in 467 patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy in EMERALD, a randomized, open-label, multicenter study (Clinical Studies [14]). Patients received ORSERDU 345 mg orally once daily (n=237) or standard of care (SOC) consisting of fulvestrant or an aromatase inhibitor (n=230). Among patients who received ORSERDU, 22% were exposed for 6 months or longer and 9% were exposed for greater than one year. (See Tables 3 and 4)</td>
</tr>
<tr>
<td>210450, 07/23/2018</td>
<td>Elagolix</td>
<td>Gynecology</td>
<td>SLCO1B1</td>
<td>Clinical Pharmacology</td>
<td>14 CLINICAL STUDIES The efficacy of ORSERDU was evaluated in EMERALD (NCT03778931), a randomized, open-label, active-controlled, multicenter trial that enrolled 478 postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer of which 228 patients had ESR1 mutations. Patients were randomized (1:1) to receive ORSERDU 345 mg orally once daily (n=239), or investigator’s choice of endocrine therapy (n=239), which included fulvestrant (n=166), or an aromatase inhibitor (n=73; anastrozole, letrozole or exemestane). Randomization was stratified by ESR1 mutation status (detected vs not detected), prior treatment with fulvestrant (yes vs no), and visceral metastasis (yes vs no). ESR1 mutational status was determined by blood circulating tumor deoxyribonucleic acid (ctDNA) using the Guardant360 CDx assay and was limited to ESR1 missense mutations in the ligand binding domain (between codons 310 to 547). Patients were treated until disease progression or unacceptable toxicity. The major efficacy outcome was progression-free survival (PFS), assessed by a blinded imaging review committee (BIRC). An additional efficacy outcome measure was overall survival (OS). A statistically significant difference in PFS was observed in the intention to treat (ITT) population and in the subgroup of patients with ESR1 mutations. An exploratory analysis of PFS in the 250 (52%) patients without ESR1 mutations showed a HR 0.86 (95% CI: 0.63, 1.19) indicating that the improvement in the ITT population was primarily attributed to the results seen in the ESR1 mutated population. Among the patients with ESR1 mutations (n=228), the median age was 63 years (range: 28-89); 100% were female; 72% were White, 5.7% Asian, 3.5% Black, 4.4% Other, 18.4% unknown/not reported; 8.8% were Hispanic/Latino; and baseline ECOG performance status was 0 (57%) or 1 (43%). Most patients had visceral disease (71%); 62% had received 1 line of endocrine therapy and 39% had received 2 lines of endocrine therapy in the advanced or metastatic setting. All patients had received prior treatment with a CDK4/6 inhibitor; 24% had received prior fulvestrant, and 25% had received prior chemotherapy in the advanced or metastatic setting. Efficacy results are presented in Table 7 and Figure 1 for patients with ESR1 mutations.</td>
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<tr>
<td>208261, 06/28/2018</td>
<td>Elbasvir and Grazoprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES The efficacy of ORSERDU was evaluated in EMERALD (NCT03778931), a randomized, open-label, active-controlled, multicenter trial that enrolled 478 postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer of which 228 patients had ESR1 mutations. Patients were required to have disease progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. Eligible patients could have received up to one prior line of chemotherapy in the advanced or metastatic setting. Patients were randomized to: ZEPATIER for 12 weeks (immediate treatment group) or standard of care (SOC) consisting of fulvestrant or an aromatase inhibitor (n=230). Among patients who received ORSERDU, 22% were exposed for 6 months or longer and 9% were exposed for greater than one year. (See Tables 3 and 4)</td>
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mass index was 26 kg/m²; 72% had baseline HCV RNA levels greater than 800,000 IU per mL; 24% had cirrhosis; 67% had non-C/C IL28B alleles (CT or TT); and 55% had genotype 1a and 45% had genotype 1b chronic HCV infection. C-EDGE CO/INFECTION was an open-label, single-arm trial in treatment-naive HCV/HIV-1 coinfected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks. Among subjects with genotype 1 infection, the median age was 50 years (range: 21 to 71); 85% of the subjects were male; 75% were White; 16% were Black or African American; 6% were Hispanic or Latin; mean body mass index was 25 kg per m²; 59% had baseline HCV RNA levels greater than 800,000 IU/mL; 16% had cirrhosis; 65% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (…)

14.3 Clinical Trials in Treatment-Experienced Subjects with Genotype 1 HCV

Treatment-Experienced Subjects who Failed Prior PegIFN with RBV Therapy (C-EDGE TE)

(…) C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 coinfection, who had prior PegIFN + RBV therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1 ratio to one of the following treatment groups: ZEPATIER for 12 weeks, ZEPATIER + RBV for 12 weeks, ZEPATIER for 16 weeks, or ZEPATIER + RBV for 16 weeks. Among subjects with genotype 1 infection, the median age was 57 years (range: 19 to 77); 64% of the subjects were male; 67% were White; 18% were Black or African American; 9% were Hispanic or Latin; mean body mass index was 28 kg/m²; 78% had baseline HCV RNA levels greater than 800,000 IU/mL; 34% had cirrhosis; 79% had non-C/C IL28B alleles (CT or TT); and 60% had genotype 1a, 39% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (…)

Treatment-Experienced Subjects who Failed Prior PegIFN + RBV + HCV Protease Inhibitor Therapy (CSALVAGE)

C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects had a median age of 55 years (range: 23 to 75); 58% of the subjects were male; 97% were White; 3% were Black or African American; 15% were Hispanic or Latin; mean body mass index was 28 kg/m²; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; and 97% had non-C/C IL28B alleles (CT or TT); 46% had baseline NS3 resistance-associated substitutions. Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and 1b subject populations, with subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions (see Microbiology [12.4]; (…)

14.4 Clinical Trial in Subjects with Genotype 1 HCV and Severe Renal Impairment including Subjects on Hemodialysis (C-SURFER)

C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m²) or CKD Stage 5 (eGFR <15 mL/min/1.73 m²), including subjects on hemodialysis, who were treatment-naive or who had failed prior therapy with IFN or PegIFN a RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR + GZR for 12 weeks (deferred treatment group). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive pharmacokinetic [PK] group). Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; and 72% had non-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.

<table>
<thead>
<tr>
<th>212273, 10/21/2019</th>
<th>Tezacaftor, Ivacaftor, and Tezacaftor</th>
<th>Pulmonary</th>
<th>CFTR</th>
<th>Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRIKAFTA is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation.</td>
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</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of TRIKAFTA for the treatment of CF in pediatric patients 12 years and older who have at least one F508del mutation in the CFTR gene was established. Use of TRIKAFTA for this indication was supported by evidence from two adequate and well-controlled studies in CF patients 12 years and older (Trial 1 and Trial 2) [see Clinical Studies (14)]. In these trials, a total of 72 adolescents (aged 12 to 17 years) received TRIKAFTA, including:

• In Trial 1, 56 adolescents who had an F508del mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor [see Adverse Reactions (6) and Clinical Studies (14)].

• In Trial 2, 16 adolescents who were homozygous for the F508del mutation [see Adverse Reactions (6) and Clinical Studies (14)].

The safety and effectiveness of TRIKAFTA in patients with CF younger than 12 years of age have not been established.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacoodynamics

Sweat Chloride Evaluation In Trial 1 (patients with an F508del mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period [see Clinical Studies (14.1)]. In Trial 2 (patients homozygous for the F508del mutation), a reduction in sweat chloride was observed from baseline at Week 4 [see Clinical Studies (14.2)].

14 CLINICAL STUDIES

Efficacy

The efficacy of TRIKAFTA in patients with CF aged 12 years and older was evaluated in two Phase 3, double blind, controlled trials (Trials 1 and 2).
<table>
<thead>
<tr>
<th>NDA/ANDA/BLA</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 205494, 08/29/2018 | Eliglustat | Inborn Errors of Metabolism | CYP2D6 | Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | \(5.1\) ECG Changes and Potential for Cardiac Arrhythmias \(7.1\) Effect of Other Drugs on CERDELGA

CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test [see Dosage and Administration (2.1)].

**INDICATIONS AND USAGE**

CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test [see Dosage and Administration (2.1)].

**2 DOSAGE AND ADMINISTRATION**

**1. Patient Selection**

Select patients with Gaucher disease type 1 based on their CYP2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype [see Indications and Usage (1)].

**2. Recommended Adult Dosage**

The recommended dosage of CERDELGA in adults is based on the patient's CYP2D6 metabolizer status. (See Table 1)

**2.3 Dosage Adjustment in EMs and IMs With or Without Hepatic Impairment and Concomitant Use of CYP2D6 or CYP3A Inhibitors**

Reduce dosage frequency of CERDELGA by 50% to once daily in CYP2D6 EMs and IMs with or without hepatic impairment taking CYP2D6 or CYP3A inhibitors, as shown in Table 2 [see Warnings and Precautions (5.1), Drug Interactions (7.1), Use in Specific Populations (8.7)].

**4 CONTRAINDICATIONS**

CERDELGA is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals.

**EMs**

- Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [see Drug Interactions (7.1)]
- Moderate or severe hepatic impairment [see Use in Specific Populations (8.7)]
- Mild hepatic impairment and taking a strong or moderate CYP2D6 inhibitor [see Use in Specific Populations (8.7)]

**IMs**

- Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [see Drug Interactions (7.1)]
- Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)]

**PMs**

- Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)]

**5 WARNINGS AND PRECAUTIONS**

**5.1 ECG Changes and Potential for Cardiac Arrhythmias**

CERDELGA is predicted to cause increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations and may increase the risk of cardiac arrhythmias.

- Use of CERDELGA is contraindicated, to be avoided, or requires dosage adjustment in patients taking CYP2D6 or CYP3A inhibitors, depending CYP2D6 metabolizer status, type of inhibitor, or degree of hepatic impairment [see Dosage and Administration (2.3), Contraindications (4), Drug Interactions (7.1)].

**7 DRUG INTERACTIONS**

**7.1 Effect of Other Drugs on CERDELGA**

Coadministration of CERDELGA with:

- CYP2D6 or CYP3A inhibitors may increase eliglustat concentrations which may increase the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac interval [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]
- Strong CYP3A inducers decreases eliglustat concentrations which may reduce CERDELGA efficacy [see Clinical Pharmacology (12.3)].

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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>

See Table 5 for prevention and management of interactions with drugs affecting CERDELGA. Use of CERDELGA is contraindicated, to be avoided, or may require dosage adjustment depending on the concomitant drug and CYP2D6 metabolizer status (see Dosage and Administration (2.2, 2.3), Contraindications (4), Drug Interactions (7.1)). (See Table 5)

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment
Use CERDELGA in patients with renal impairment based on the patient’s CYP2D6 metabolizer status [see Clinical Pharmacology (12.3)].

EMs
- Avoid CERDELGA in patients with end-stage renal disease (ESRD) (estimated creatinine clearance (eCLcr) less than 15 mL/min not on dialysis or requiring dialysis).
- No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment (eCLcr at least 15 mL/min).

IMs and PMs
- Avoid CERDELGA in patients with any degree of renal impairment.

8.7 Hepatic Impairment
Use CERDELGA in patients with hepatic impairment based on CYP2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors [see Clinical Pharmacology (12.3)].

EMs
- CERDELGA is contraindicated in patients with [see Contraindications (4)]: o severe (Child-Pugh Class C) hepatic impairment o moderate (Child-Pugh Class B) hepatic impairment o mild (Child-Pugh Class A) hepatic impairment taking a strong or moderate CYP2D6 inhibitor
- Reduce dosage frequency of CERDELGA 84 mg to once daily [see Dosage and Administration (2.3)] in patients with mild hepatic impairment taking: o a weak CYP2D6 inhibitor o a strong, moderate, or weak CYP3A inhibitor
- No dosage adjustment is recommended in patients with mild hepatic impairment, unless otherwise specified above.

IMs and PMs
- CERDELGA is contraindicated in patients with any degree of hepatic impairment [see Contraindications (4)].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption
The oral bioavailability of eliglustat was less than 5% in CYP2D6 EMs following a single 84 mg dose of CERDELGA.
In CYP2D6 EMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose-proportional manner over the dose range of 42 to 254 mg (0.5 to 3.5 times the recommended dosage). In addition, after multiple oral doses of 84 mg twice daily in EMs, eliglustat systemic exposure (AUC0-12) increased up to about 2-fold at steady state compared to after the first dose (AUC0-12). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7-fold to 9-fold higher in PMs.

Dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted Cmax and AUC0-24hr in PMs using a physiologically based pharmacokinetic (PBPK) model with 84 mg once daily were 75 ng/mL and 956 hr∙ng/mL, respectively.

Table 7 describes the pharmacokinetic parameters for eliglustat in healthy subjects following multiple doses of 84 mg CERDELGA twice daily. (See Table 7) Administration of CERDELGA with a high fat meal (approximately 1000 calories with 50% calories from fat) resulted in a 15% decrease in Cmax (not clinically significant) but no change in AUC.

Distribution
Following intravenous administration, the volume of distribution of eliglustat was 835 L in EMs. Plasma protein binding of eliglustat ranges from 76% to 83%.

Elimination
Eliglustat terminal elimination half-life was approximately 6.5 hours in CYP2D6 EMs, and 8.9 hours in PMs. Following intravenous administration of 42 mg (0.5 times the recommended oral dose) in healthy subjects, the mean (range) of eliglustat total body clearance was 88 L/h (80 to 105 L/h) in EMs.

Specific Populations
No clinically significant differences in the pharmacokinetics of eliglustat were observed based on age (18 to 71 years), sex, race (mostly were Caucasian, including those of Ashkenazi Jewish descent; however, it included the following populations: African American, American Indians, Hispanics, and Asians), or body weight (41 to 136 kg).

Patients with renal impairment
Eliglustat pharmacokinetics was similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs. Eliglustat pharmacokinetics in EMs with ESRD and in IMs or PMs with any degree of renal impairment is unknown [see Use in Specific Populations (8.6)].

Patients with hepatic impairment
Table 8 describes the effect of mild and moderate hepatic impairment on the pharmacokinetics of eliglustat in CYP2D6 EMs compared to EMs with normal hepatic function following a single 84 mg dose. The effect of hepatic impairment is highly variable with the coefficients of variation (CVs%) of 135% and 110% for Cmax and 171% and 121% for AUC in CYP2D6 EMs with mild and moderate hepatic impairment, respectively. (See Table 8) Steady-state pharmacokinetics of eliglustat in CYP2D6 IMs and PMs with mild and moderate hepatic impairment is unknown. The effect of severe hepatic impairment in subjects with any CYP2D6 phenotype is unknown (see Use in Specific Populations (8.7)).

Drug Interaction Studies
Effect of other drugs on CERDELGA
Table 9 describes the effect of drug interactions on the pharmacokinetics of eliglustat [see Drug Interactions (7.1)]. (See Table 9)

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>125460, 02/14/2014</td>
<td>Elgosulfase</td>
<td>Inborn Errors of Metabolism</td>
<td>GALNS</td>
<td>Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>Vimizim (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).</td>
</tr>
<tr>
<td>761345, 08/14/2023</td>
<td>Elranatamab-bccm (1)</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>761345, 08/16/2023</td>
<td>Elranatamab-bccm (2)</td>
<td>Oncology</td>
<td>Chromosome 4p/14q</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
</tr>
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| NDA/ANDA/BLA Number, Label Version Date | Drug | Therapeutic Area | Biomarker(s) | Labeling Sections | Labeling Text
|---|---|---|---|---|---
| 761345, 08/14/2023 | Elranatamab-bcm (3) | Oncology | Chromosome 14q:16q | Clinical Studies | 14 CLINICAL STUDIES
14.1 Relapsed or Refractory Multiple Myeloma The 123 patients enrolled in pivotal Cohort A had received a median of 5 prior lines of therapy (range: 2 to 22). Ninety-seven patients who were not exposed to prior BCMA-directed therapy and received at least one prior line of therapy comprised the efficacy population. Among the 57 patients in the efficacy population, the median age was 69 (range: 46 to 89) years with 18.6% of patients 75 years of age. Forty percent were female; 59.8% were White, 13.4% were Asian, 7.2% were Hispanic/Latino, 5.2% were Black or African American. Disease stage (R-ISS) at study entry was 20.6% in Stage I, 53.6% in Stage II, and 17.6% in Stage III. The median time since initial diagnosis of multiple myeloma to enrollment was 79.6 (range: 16 to 228) months. 94.8% were refractory to their last line of therapy, 89.1% received prior autologous stem cell transplantation, and 7.2% received prior allogeneic stem cell transplantation. High-risk cytogenetics [4q:14], [14:16], or [del(17p)] were present in 22.7% of patients. 34.0% of patients had extramedullary disease at baseline by BICR. (…)

| 022291, 04/29/2020 | Eltrombopag (1) | Hematology | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.3 Thrombotic/Thromboembolic Complications Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). (…)

| 022291, 04/29/2020 | Eltrombopag (2) | Hematology | SERPINC1 (Antithrombin III) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.3 Thrombotic/Thromboembolic Complications Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). (…)

| 022291, 04/29/2020 | Eltrombopag (3) | Hematology | Chromosome 7 | Adverse Reactions | 6 ADVERSE REACTIONS
6.1 Clinical Trials Experience Cytophenic Abnormalities In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M6 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality; 7 patients had the loss of chromosome 7, 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13, and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA. (…)

| 022291, 04/29/2020 | Eltrombopag (4) | Hematology | Chromosome 13 | Adverse Reactions | 6 ADVERSE REACTIONS
6.1 Clinical Trials Experience Cytophenic Abnormalities In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M6 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality; 7 patients had the loss of chromosome 7, 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13, and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA. (…)

| 761107, 11/20/2018 | Ematumab-izag | Hematology | PRF1, RA2B7A, SHD1A, STXB2, STX11, UNC13D, XIAP (Hemophagocytic Lymphohistiocytosis) | Clinical Studies | 14 CLINICAL STUDIES
(…) A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FHHL3-UNC13D (MUNC 13-4) (26%), FHHL2-PRF1 (19%), and Griscelli Syndrome type 2 (19%). The HLH mutations in the population enrolled are described in Table 3. (See Table 3)

| 209606, 09/27/2019 | Enasidenib | Oncology | IDH2 | 1 INDICATIONS AND USAGE
1.1 Acute Myeloid Leukemia IDH2/IDH1 is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection

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<tr>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
<td>1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma</td>
<td></td>
<td></td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
<td>Select patients for the treatment of AML with IDHIFA based on the presence of IDH2 mutations in the blood or bone marrow [see Indications and Usage (1.1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
</tr>
<tr>
<td>1.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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<tr>
<td>1.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>1.4 Limitations of Use</td>
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<td>BRAF</td>
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<tr>
<td>BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC [see Warnings and Precautions (5.2)].</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection</td>
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<td>BRAF</td>
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<tr>
<td>Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI [see Warnings and Precautions (5.2), Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<tr>
<td>Confirm the presence of a BRAF V600E mutation in tumor specimens prior to initiating BRAFTOVI [see Warnings and Precautions (5.2), Clinical Studies (14.2)]. Information on FDA-approved tests for the detection of BRAF V600E mutations in CRC is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>2.2 Recommended Dosage for BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma and for BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)</td>
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<tr>
<td>The recommended dosage of BRAF V600E is 450 mg (six 75 mg capsules) orally once daily in combination with cetuximab until disease progression or unacceptable toxicity. Refer to the cetuximab prescribing information for recommended cetuximab dosing information.</td>
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<tr>
<td>2.3 Recommended Dosage for BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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<td>BRAF</td>
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<tr>
<td>The recommended dosage of BRAFTOVI is 300 mg (four 75 mg capsules) orally once daily in combination with cetuximab until disease progression or unacceptable toxicity. Refer to the cetuximab prescribing information for recommended cetuximab dosing information.</td>
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<tr>
<td>2.5 Dosage Modifications for Adverse Reactions</td>
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<td>BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC [see Warnings and Precautions (5.2)].</td>
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<th>Therapeutic Biomarker †</th>
<th>Labeling Sections</th>
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</table>

If bimetinib is withheld, reduce BRAFV0I to a maximum dose of 300 mg (four 75 mg capsules) once daily until bimetinib is resumed [see Warnings and Precautions (5.9)]. Dose reductions for adverse reactions associated with BRAFV0I are presented in Table 1. BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) If cetuximab is discontinued, discontinue BRAFV0I. Dose reductions for adverse reactions associated with BRAFV0I are presented in Table 2. BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma, BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC), or BRAF V600E Mutation-Positive NSCLC. Dosage modifications for adverse reactions associated with BRAFV0I are presented in Table 3.

5 WARNINGS AND PRECAUTIONS

5.2 Tumor Promotion in BRAF Wild-Type Tumors
In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation prior to initiating BRAFV0I [see Indications and Usage (1), Dosage and Administration (2.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
(…) The safety of BRAFV0I in combination with bimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFV0I (450 mg once daily) in combination with bimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS). (…) BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
The safety of BRAFV0I in combination with cetuximab (400 mg/m² initial dose, followed by 250 mg/m² weekly) was evaluated in 216 patients with BRAF V600E mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BEACON CRC). (…) BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)
The safety of BRAFV0I in combination with bimetinib was evaluated in 581 patients with BRAF V600E mutation-positive metastatic NSCLC who received BRAFV0I (450 mg once daily) in combination with bimetinib (45 mg twice daily) in an open-label, single-arm trial (PHAROS).

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use
Of the 695 patients with BRAF mutation-positive melanoma who received BRAFV0I in combination with bimetinib across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older [see Clinical Studies (14.1)]. Of the 216 patients with BRAF V600E mutation-positive metastatic CRC who received BRAFV0I in combination with cetuximab, 62 (29%) were 65 years of age to up to 75 years of age, while 20 (9%) were 75 years of age and over [see Clinical Studies (14.2)]. Of the 98 patients with BRAF V600E mutation-positive metastatic NSCLC who received BRAFV0I with bimetinib, 62 (63%) were 65 years of age and over and 20 (20%) were 75 years and over [see Clinical Studies (14.3)]. No overall differences in the safety or effectiveness of BRAFV0I plus bimetinib or BRAFV0I plus cetuximab were observed in older patients as compared to younger patients.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics
The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation. BRAF V600E mutation-positive metastatic CRC. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg (0.1 to 1.6 times the maximum recommended dose of 450 mg). After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg (0.1 to 1.8 times the maximum recommended dose of 450 mg). Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1. Intersubject variability (CV%) of AUC ranged from 12% to 69%.

14 CLINICAL STUDIES

14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
BRAFV0I in combination with bimetinib was evaluated in a randomized, active-controlled, open-label multicenter trial (COLUMBUS: NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. (…) Based on centralized testing, 100% of patients’ tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (+1%). (…) BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
BRAFV0I in combination with cetuximab was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC: NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen BRAF V600E RQ polymerase chain reaction (PCR) Kit. With disease progression after 1 or 2 prior regimens. (…) BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer
BRAFV0I in combination with bimetinib was evaluated in an open-label, multicenter, single-arm study in patients with BRAF V600E mutation-positive metastatic non-small cell lung cancer (NSCLC) (PHAROS: NCT03915951). Eligible patients had a diagnosis of histologically-confirmed metastatic NSCLC with BRAF V600E mutation that was treatment-naïve or had been previously treated with 1 prior line of systemic therapy in the metastatic setting (platinum-based treatment-naïve).

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<th>Labeling Text§</th>
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| 210496, 10/13/2023                     | Encorafenib (2) | Oncology | RAS | Dosage and Administration, Warnings and Precautions, Clinical Studies | 2 DOSAGE AND ADMINISTRATION  
2.5 Dosage Modifications for Adverse Reactions  
BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma, BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC), or BRAF V600E Mutation-Positive NSCLC  
Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 3. |
| 212725, 10/20/2023                     | Entrectinib (1) | Oncology | ROS1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 ROS1-Positive Non-Small Cell Lung Cancer  
ROZLYTREK is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.  
2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Select patients for the treatment of metastatic NSCLC with ROZLYTREK based on the presence of ROS1 rearrangement(s) in tumor specimens. An FDA-approved test for detection of ROS1 rearrangement(s) in NSCLC is not available. |

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<th>Labeling Text‡</th>
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</table>
| 212725, 10/20/2023                     | Entrectinib (2) | Oncology          | NTRK       | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE

**14 CLINICAL STUDIES**

**14.1 ROS1-Positive Non-Small Cell Lung Cancer**

The efficacy of ROZLYTREK was evaluated in a pooled subgroup of patients with ROS1-positive metastatic NSCLC who received ROZLYTREK at various doses and schedules (10%) received ROZLYTREK 600 mg orally once daily) and were enrolled in one of three multicenter, single-arm, open-label clinical trials: ALKA, STARTRK-1 (NCT02079810) and STARTRK-2 (NCT02058907). To be included in this pooled subgroup, patients were required to have histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG performance status ≤ 2, measurable disease per RECIST v1.1, ≥ 18 months of follow-up from first post-therapy tumor assessment, and no prior therapy with a ROS1 inhibitor. Identification of ROS1 gene fusion in tumor specimens was prospectively determined in local laboratories using either a fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), or polymerase chain reaction (PCR) laboratory-developed tests. All patients were assessed for CNS lesions at baseline. The overall efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR). Intracranial response according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) was assessed by BICR. Tumor assessments with imaging were performed every 8 weeks. Efficacy was assessed in 92 patients with ROS1-positive NSCLC. The median age was 53 years (range: 27 to 80); female (65%); White (48%), Asian (45%), and Black (15%); and Hispanic or Latino (24.4%); never smoked (59%); and ECOG performance status 0 or 1 (88%). Ninety-nine percent of patients had metastatic disease, including 42% with CNS metastases; 96% had adenocarcinomas; 65% received prior platinum-based chemotherapy for metastatic or recurrent disease and no patient had progressed in less than 6 months following platinum-based adjuvant or neoadjuvant therapy. ROS1 positivity was determined by NGS in 79%, FISH in 16%, and PCR in 4%. Twenty-five percent had central laboratory confirmation of ROS1 positivity using an analytically validated NGS test.

Efficacy results are summarized in Table 13.

**1.3 NTRK Gene Fusion-Positive Solid Tumors**

ROZLYTREK is indicated for the treatment of adult and pediatric patients older than 1 month of age with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have either progressed following treatment or have no satisfactory alternative therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response (see Clinical Studies (14.2)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**2 DOSE ADMINISTRATION**

**2.1 Patient Selection**

- Select patients for the treatment of metastatic NSCLC with ROZLYTREK based on the presence of ROS1 rearrangement(s) in tumor or plasma specimens (see Clinical Studies (14.1)). Testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing. Information on FDA-approved tests for the detection of ROS1 rearrangement(s) in NSCLC is available at http://www.fda.gov/CompanionDiagnostics.
- Select patients for treatment of locally advanced or metastatic solid tumors with ROZLYTREK based on the presence of a NTRK gene fusion in tumor or plasma specimens (see Clinical Studies (14.2)). Testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing. Information on FDA-approved tests for the detection of NTRK gene fusion(s) in solid tumors is available at http://www.fda.gov/CompanionDiagnostics.

**2.3 Recommended Dosage for NTRK Gene Fusion-Positive Solid Tumors**

**Adults**

The recommended dosages of ROZLYTREK for the treatment of adult and pediatric patients with NTRK Gene Fusion-Positive Solid Tumors are provided in Table 1. The recommended dosages of ROZLYTREK for the treatment of pediatric patients older than 6 months with NTRK Gene Fusion-Positive Solid Tumors is provided in Table 2.

**6 AVERSE REACTIONS**

**6.1 Clinical Trial Experience**

- (…) ROS1 gene fusions were present in 42% and NTRK gene fusions were present in 20%. Most adults (75%) received ROZLYTREK 600 mg orally once daily. (…) Safety in Pediatric Patients

The safety of ROZLYTREK was evaluated in patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label clinical trials: STARTRK-NG (n=68), TAPISTRY (n=6) and STARTRK-2 (n=2). (…) Safety of ROZLYTREK was evaluated in patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label clinical trials: STARTRK-NG (n=68), TAPISTRY (n=6) and STARTRK-2 (n=2). (…)

**8 USE IN SPECIFIC POPULATIONS**

**8.4 Pediatric Use**

The safety and effectiveness of ROZLYTREK in pediatric patients aged 12 years and older with solid tumors that have an NTRK gene fusion have been established. The effectiveness of ROZLYTREK in adolescent patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumors harboring an NTRK gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacokinetic data in adolescents enrolled in STARTRK-NG. (…) The safety and effectiveness of ROZLYTREK in pediatric patients less than 12 years of age with solid tumors who have an NTRK gene fusion have not been established.

**NTRK Gene Fusion-Positive Solid Tumors**

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have either progressed following treatment or have no satisfactory alternative therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response (see Clinical Studies (14.2)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
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<td>217388, 12/21/2023</td>
<td>Epilontersen</td>
<td>Neurology</td>
<td>TTR</td>
<td>Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
</tr>
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</table>

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The pharmacokinetics for entrectinib and its pharmacologically active major circulating metabolite M5 were characterized in adult patients with ROS1-positive NSCLC, NTRK gene fusion-positive solid tumors, and healthy subjects. (…)

14 CLINICAL STUDIES

14.2 NTRK Gene Fusion-Positive Solid Tumors

Efficacy in Adult Patients

The efficacy of ROZLYTREK was evaluated in a pooled subgroup of adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, single-arm, open-label clinical trials: ALKA, STARTK-1 (NCT02097810) and STARTK-2 (NCT02568207). To be included in this pooled subgroup, patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease; measurable disease per RECIST v1.1; at least 2 years of follow-up from first post-treatment tumor assessment; and no prior therapy with a TRK inhibitor. Patients received ROZLYTREK at various doses and schedules (94% received ROZLYTREK 600 mg orally once daily) until unacceptable toxicity or disease progression. Identification of positive NTRK gene fusion status was prospectively determined in local laboratories or a central laboratory using various nucleic acid-based tests. The major efficacy outcome measures were ORR and DOR, as determined by a BICR according to RECIST v1.1. Intracranial response according to RECIST v1.1 as evaluated by BICR. Tumor assessments with imaging were performed every 8 weeks.

Efficacy was assessed in the first 54 adult patients with solid tumors with an NTRK gene fusion enrolled into these trials. The median age was 58 years (range: 21 to 83); female (69%); White (80%), Asian (13%) and Hispanic or Latino (7%); and ECOG performance status 0 (43%) or 1 (46%). Ninety-six percent of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced; unresectable disease. All patients had received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), or systemic therapy (n = 48). Forty patients (74%) received prior systemic therapy for metastatic disease with a median of 1 prior systemic regimen and 17% (n = 9) received 3 or more prior systemic regimens. The most common cancers were sarcoma (24%), lung cancer (19%), salivary gland tumors (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%). A total of 52 (96%) patients had an NTRK gene fusion detected by NGS and 2 (4%) had an NTRK gene fusion detected by other nucleic acid-based tests. Eighty-three percent of patients had central laboratory confirmation of NTRK gene fusion using an analytically validated NGS test.

Efficacy results are summarized in Tables 13, 14, and 15.

Efficacy in Pediatric Patients

The efficacy of ROZLYTREK was evaluated in pediatric patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of two multicenter, open-label clinical trials: STARTK-NG (NCT02650401) and TAPISTRY (NCT04589845). To be included in the analysis, patients were required to have received at least 1 dose of ROZLYTREK: measurable or evaluable disease at baseline; at least 6 months of follow-up; and no prior therapy with a TRK inhibitor. Patients received ROZLYTREK 20 mg to 600 mg based on body surface area (BSA) orally or via enteral feeding tube once daily in 4-week cycles until unacceptable toxicity or disease progression. The major efficacy outcome measure was overall response rate (ORR) as assessed by BICR according to RECIST v1.1 for extracranial tumors and according to Response Assessment in Neuro-Oncology (RANO) for primary central nervous system (CNS) tumors. An additional efficacy outcome measure was DOR as evaluated by BICR.

Efficacy was assessed in 33 pediatric patients with NTRK fusion-positive solid tumors treated with ROZLYTREK. The median age was 4 years (range: 2 months to 15 years); male (52%); White (58%), Asian (30%), other races (9%), Black or African American (3.0%), and Hispanic or Latino (9%). Seventy-one percent of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior therapy for their cancer including surgery (n = 43), radiotherapy (n = 36), and/or systemic therapy (n = 48). Forty patients (74%) received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), and/or systemic therapy (n = 48). The sites for metastatic disease included other (4 patients), brain (3 patients) and lung (2 patients).

Efficacy results are summarized in Tables 16 and 17.

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| 212018, 04/02/2020                     | Erdafitinib (1) | Oncology | FGFR | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies, Patient Counseling Information | BALVERSATM is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), that has:  
- susceptible FGFR3 or FGFR2 genetic alterations, and  
- progressed during or following at least one prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.  
Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA [see Dosage and Administration (2.1) and Clinical Studies (14)]. |
| 212018, 04/12/2019                    | Erdafitinib (2) | Oncology | CYP2C9 | Use in Specific Populations, Clinical Pharmacology | 8 USE IN SPECIFIC POPULATIONS  
8.6 CYP2C9 Poor Metabolizers  
CYP2C9*3/*3 Genotype: Erdafitinib plasma concentrations were predicted to be higher in patients with the CYP2C9*3/*3 genotype. Monitor for increased adverse reactions in patients who are known or suspected to have CYP2C9*3/*3 genotype [see Pharmacogenomics (12.5)]. |
| 201532, 10/19/2016                    | Eribulin (1) | Oncology | ERBB2 (HER2) | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Metastatic Breast Cancer |

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<td>201532, 10/19/2016</td>
<td>Erbulin (2)</td>
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<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Metastatic Breast Cancer</td>
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<td>(...) Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER, PR, HER2/neu - : 19%), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (...)</td>
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<td>021743, 10/18/2016</td>
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<td>EGFR</td>
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<td>1.1 Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>TARCEVA® is indicated for:</td>
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<td>• The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen [see Clinical Studies (14.1, 14.3)].</td>
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<td>Limitations of use:</td>
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<td>• Safety and efficacy of TARCEVA have not been established in patients with NSCLC whose tumors have other EGFR mutations [see Clinical Studies (14.1, 14.2)].</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Selection of Patients with Metastatic NSCLC</td>
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<td>Select patients for the treatment of metastatic NSCLC with TARCEVA based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor or plasma specimens [See Clinical Studies (14.1, 14.2)]. If these mutations are not detected in a plasma specimen, test tumor tissue if available. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a></td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trial Experience</td>
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<td>First-Line Treatment of Patients with EGFR Mutations</td>
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<td>The most frequent (≥ 30%) adverse reactions in TARCEVA-treated patients were diarrhea, asthenia, rash, cough, dyspnea, and decreased appetite. In TARCEVA-treated patients the median time to onset of rash was 15 days and the median time to onset of diarrhea was 32 days. (...)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Non-Small Cell Lung Cancer (NSCLC) – First-Line Treatment of Patients with EGFR Mutations</td>
</tr>
<tr>
<td>Study 1</td>
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<td>Study 1</td>
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<td>The safety and efficacy of TARCEVA as monotherapy for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or exon 21 (L858R) substitution mutations was demonstrated in Study 1, a randomized, open label, clinical trial conducted in Europe. One hundred seventy-four (174) White patients were randomized 1:1 to receive erlotinib 150 mg once daily until disease progression (n = 86) or four cycles of a standard platinum-based doublet chemotherapy (n = 88); standard chemotherapy regimens were cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. Randomization was stratified by EGFR mutation (exon 19 deletion or exon 21 (L858R) substitution) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1 to 2). EGFR mutation status for screening and enrollment of patients was determined by a clinical trials assay (CTA). Tumor samples from 134 patients (69 patients from the erlotinib arm and 65 patients from the chemotherapy arm) were tested retrospectively by the FDA-approved companion diagnostic, cobas® EGFR Mutation Test. (...)</td>
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<td>(...) The disease characteristics were 93% Stage IV and 7% Stage IIB with pleural effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition), 93% adenocarcinoma, 66% exon 19 mutation deletions and 34% exon 21 (L858R) point mutation by CTA. (...)</td>
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<td>In exploratory subgroup analyses based on EGFR mutation subtype, the hazard ratio (HR) for PFS was 0.27 (95% CI 0.17 to 0.43) in patients with exon 19 deletions and 0.52 (95% CI 0.29 to 0.95) in patients with exon 21 (L858R) substitution. The HR for OS was 0.84 (95% CI 0.57 to 1.24) in the exon 19 deletion subgroup and 0.99 (95% CI 0.56 to 1.76) in the exon 21 (L858R) substitution subgroup.</td>
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<td></td>
<td>14.2 NSCLC - Lack of Efficacy of TARCEVA in Maintenance Treatment of Patients without EGFR Mutations</td>
</tr>
<tr>
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<td>Lack of efficacy of TARCEVA for the maintenance treatment of patients with NSCLC without EGFR activating mutations was demonstrated in Study 2. Study 2 was a multicenter, placebo-controlled, randomized trial of 643 patients with advanced NSCLC without an EGFR exon 19 deletion or exon 21 L858R mutation who had not experienced disease progression after four cycles of platinum-based chemotherapy. (...)</td>
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<td>14.3 NSCLC– Maintenance Treatment or Second/Third Line Treatment</td>
</tr>
</tbody>
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<tr>
<td>062759</td>
<td>Erythromycin and Sulfisoxazole</td>
<td>Infectious Diseases</td>
<td>G6PD Precautions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<tr>
<td>021323, 01/11/2019</td>
<td>Escitalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2D6 Drug Interactions</td>
<td>7 DRUG INTERACTIONS</td>
<td></td>
</tr>
<tr>
<td>021323, 01/11/2019</td>
<td>Escitalopram (2)</td>
<td>Psychiatry</td>
<td>CYP2C19 Adverse Reactions</td>
<td>6 ADVERSE REACTIONS</td>
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<tr>
<td>022101, 03/04/2022</td>
<td>Esomeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19 Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
<td></td>
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<tr>
<td>009402, 02/16/2022</td>
<td>Estradiol Valerate</td>
<td>Gynecology</td>
<td>ESR, PGR (Hormone Receptor) Warnings</td>
<td>WARNINGS</td>
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<tr>
<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (1)</td>
<td>Gynecology</td>
<td>PROC Contraindications</td>
<td>4 CONTRAINDICATIONS</td>
<td></td>
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<tr>
<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (2)</td>
<td>Gynecology</td>
<td>PROS1 Contraindications</td>
<td>4 CONTRAINDICATIONS</td>
<td></td>
</tr>
<tr>
<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (3)</td>
<td>Gynecology</td>
<td>SERPINC1 (Antithrombin III) Contraindications</td>
<td>4 CONTRAINDICATIONS</td>
<td></td>
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<tr>
<td>206488, 10/11/2018</td>
<td>Etoposide</td>
<td>Neurology</td>
<td>DMD Indications and Usage, Adverse Reactions, Use in Specific</td>
<td>1 INDICATIONS AND USAGE</td>
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Two randomized, double-blind, placebo-controlled trials, Studies 3 and 4, examined the efficacy and safety of Tarecula administered to patients with metastatic NSCLC as maintenance therapy after initial treatment with chemotherapy (Study 3) or with disease progression following initial treatment with chemotherapy (Study 4). Determination of EGFR mutation status was not required for enrollment, (...) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…)

In vitro studies did not reveal an inhibitory effect of esomeprazole on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with esomeprazole, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on esomeprazole metabolism. (…)

Pharmacogenomics CYP2C19, a polymorphic enzyme, is involved in the metabolism of esomeprazole. The CYP2C19*1 allele is functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are extensive metabolizers and those carrying two loss-of-function alleles are poor metabolizers. The systemic exposure to esomeprazole varies with a patient’s metabolism status: poor metabolizers > intermediate metabolizers > extensive metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers. Systemic esomeprazole exposures were modestly higher (approximately 17%) in CYP2C19 intermediate metabolizers (IM; n=6) compared to extensive metabolizers (EM; n=17) of CYP2C19. Similar pharmacokinetic differences were noted across these genotypes in a study of Chinese healthy subjects that included 7 EMs and 11 IMs. There is very limited pharmacokinetic information for poor metabolizers (PM) from these studies. All steady state following once daily administration of esomeprazole 40 mg, the ratio of AUC in poor metabolizers to AUC in the rest of the population (EMs) from these groups. (…) Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups. (…)

TARCEVA administered to patients with metastatic NSCLC as maintenance therapy after initial treatment with chemotherapy (Study 3) or with disease progression following initial treatment with chemotherapy (Study 4). Determination of EGFR mutation status was not required for enrollment, (...) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…) Determination of EGFR mutation status was not required for enrollment, (...) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…)

Similar pharmacokinetic differences were noted across these genotypes in a study of Chinese healthy subjects that included 7 EMs and 11 IMs. There is very limited pharmacokinetic information for poor metabolizers (PM) from these studies. All steady state following once daily administration of esomeprazole 40 mg, the ratio of AUC in poor metabolizers to AUC in the rest of the population (EMs) is approximately 1.5. This change in exposure is not considered clinically meaningful.

Etoposide administered to patients with chemotherapy (Study 3) or with disease progression following initial treatment with chemotherapy (Study 4). Determination of EGFR mutation status was not required for enrollment, (...) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…)

Similar pharmacokinetic differences were noted across these genotypes in a study of Chinese healthy subjects that included 7 EMs and 11 IMs. There is very limited pharmacokinetic information for poor metabolizers (PM) from these studies. All steady state following once daily administration of esomeprazole 40 mg, the ratio of AUC in poor metabolizers to AUC in the rest of the population (EMs) is approximately 1.5. This change in exposure is not considered clinically meaningful.

TARCEVA administered to patients with metastatic NSCLC as maintenance therapy after initial treatment with chemotherapy (Study 3) or with disease progression following initial treatment with chemotherapy (Study 4). Determination of EGFR mutation status was not required for enrollment, (...) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…)

Similar pharmacokinetic differences were noted across these genotypes in a study of Chinese healthy subjects that included 7 EMs and 11 IMs. There is very limited pharmacokinetic information for poor metabolizers (PM) from these studies. All steady state following once daily administration of esomeprazole 40 mg, the ratio of AUC in poor metabolizers to AUC in the rest of the population (EMs) is approximately 1.5. This change in exposure is not considered clinically meaningful.

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<tr>
<td>216956, 10/12/2023</td>
<td>Etrasimod</td>
<td>Gastroenterology</td>
<td>CYP2C9</td>
<td>Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>CYP2C9 Poor Metabolizers Using Moderate to Strong Inhibitors of CYP2C8 or CYP3A4. Concomitant use of moderate to strong inhibitors of CYP2C8 or CYP3A4 is expected with concomitant use of moderate to strong inhibitors of CYP2C8 or CYP3A4 (see Clinical Pharmacology (12.3, 12.5)). Prevention or Management: Concomitant use not recommended.</td>
</tr>
<tr>
<td>022334, 02/13/2020</td>
<td>Everolimus (1)</td>
<td>Oncology</td>
<td>ERBB2/ HER2</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer</td>
<td>AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2 negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.</td>
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<td>2.2 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer</td>
<td>The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<tr>
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<td>5.7 Geriatric Patients</td>
<td>In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients &lt; 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients &lt; 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended (see Dosage and Administration (2.2), Use in Specific Populations (8.5)).</td>
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<td></td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td></td>
<td></td>
<td>6.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer</td>
<td>The safety of AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily) (n = 485) vs. placebo in combination with exemestane (n = 239) was evaluated in a randomized, controlled trial (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (28 to 93 years), and 75% were White. The median follow-up was approximately 13 months.</td>
</tr>
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<td>022334, 02/13/2020</td>
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<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>In a single arm study (SWISH; N = 92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily), patients started dexamethasone 0.5 mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with AFINITOR and exemestane. (…)</td>
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<tbody>
<tr>
<td>02/11/2021, 761181</td>
<td>Evinacumab-dgnb</td>
<td>Endocrinology</td>
<td>LDLR</td>
<td>Clinical Studies</td>
<td><em>(1)</em> The concomitant administration of evinacumab with a statin resulted in a significant increase in LDL-C reduction. <em>(2)</em> The effects of evinacumab on cardiovascular morbidity and mortality have not been determined.</td>
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<tr>
<td>02/11/2021, 761181</td>
<td>Evinacumab-dgnb</td>
<td>Endocrinology</td>
<td>Nonspecific (Homozygous Familial Hypercholesterolemia)</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td><em>(2)†</em> The effects of evinacumab on cardiovascular morbidity and mortality have not been determined. <em>(3)‡</em> Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.</td>
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| 125522, 08/8/2022                      | Evolocumab (1) | Endocrinology | Nonspecific (Heterozygous Familial Hypercholesterolemia) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | Pediatric Patients
A 15-year-old patient with HoFH received evinacumab-dgnb at 15 mg/kg IV every 4 weeks. Steady-state trough and end-of-infusion concentrations were within the range observed in adult patients. Drug Interaction Studies Drug interaction studies have not been conducted with evinacumab-dgnb. In a clinical trial, the concentrations of statins (atorvastatin, rosuvastatin, simvastatin) were not meaningfully altered in patients taking statins prior to and post administration of evinacumab-dgnb. Concentrations of evinacumab-dgnb were comparable in patients with HoFH taking or not taking background lipidlowering therapy.

14 CLINICAL STUDIES
Study ELIPSE-HoFH (NCT03399786) was a multicenter, double-blind, randomized, placebocontrolled trial evaluating the efficacy and safety of EVKEEEZA compared to placebo in 65 patients with HoFH. During the 24-week, double-blind treatment period, 43 patients were randomized to receive EVKEEEZA 15 mg/kg IV every 4 weeks and 22 patients to receive placebo. After the double-blind treatment period, 64 of 65 patients entered a 24-week open-label extension period in which all patients received EVKEEEZA 15 mg/kg IV every 4 weeks. Patients were on a background of other lipid-lowering therapies, including maximally tolerated statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis. Enrolment was stratified by apheresis status and geographical region. The diagnosis of HoFH was determined by genetic testing or by the presence of the following clinical criteria: history of an untreated total cholesterol (TC) >500 mg/dL and either xanthoma before 10 years of age or evidence of TC >250 mg/dL in both parents. In this trial, 40% (26 of 65) patients had limited LDL receptor (LDLR) function, defined by either <15% receptor function by in vitro assays or by genetic variants likely to result in minimal to no LDLR function by mutation analysis. (See Table 2 and Figure 1)

Pediatric Patients with HoFH
In ELIPSE-HoFH, 1 pediatric patient received 15 mg/kg IV of EVKEEEZA every 4 weeks, and 1 pediatric patient received placebo, as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, PCSK9 inhibitor antibodies and lipoprotein apheresis). Both patients had null/null variants in the LDLR. At Week 24, the percent change in LDL-C with EVKEEEZA was −73% and with placebo was +6%. In an open-label extension study, 13 pediatric patients with HoFH (12 to 17 years of age) received 15 mg/kg IV of EVKEEEZA every 4 weeks as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, PCSK9 inhibitor antibodies and lipoprotein apheresis) for a median treatment duration of 33 weeks. The mean percent change from baseline in LDL-C at Week 24 was −52% in the 9 patients who completed treatment and had a lipid assessment at Week 24. Overall, the effect of evinacumab-dgnb on lipid parameters in pediatric patients with HoFH was generally similar to that seen in adults with HoFH.

2 INDICATIONS AND USAGE
REPATHA is indicated (…) • As an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C • As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
• In pediatric patients aged 10 years and older with HeFH:
  o The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously [see Dosage and Administration (2.3)].
  o If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

6 ADVERSE REACTIONS
Adverse Reactions in Pediatric Patients with HeFH
In a 24-week, randomized, placebo-controlled, double-blind trial of 157 pediatric patients with HeFH, 104 patients received 420 mg REPATHA subcutaneously once monthly (see Clinical Studies (14)). The mean age was 13.7 years (range: 10 to 17 years), 56% were female, 85% White, 1% Black, 1% Asian, and 13% other; 8% identified as Hispanic ethnicity. Common adverse reactions (> 5% of patients treated with REPATHA and occurring more frequently than placebo) included:
  • Nasopharyngitis (12% versus 11%)
  • Headache (11% versus 2%)
  • Oropharyngeal pain (7% versus 0%)
  • Influenza (6% versus 4%)
  • Upper respiratory tract infection (6% versus 2%)

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of REPATHA as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HeFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is based on data from a 24-week, randomized, placebo-controlled, double-blind trial in pediatric patients with HeFH. In the trial, 104 patients received REPATHA 420 mg subcutaneously once monthly and 53 patients received placebo; 39 patients (25%) were 10 to 11 years of age (see Adverse Reactions (6.1) and Clinical Studies (14)). The safety and effectiveness of REPATHA have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years old or in pediatric patients with other types of hyperlipidemia.

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<td>125522, 08/06/2022</td>
<td>Evolocumab (2)</td>
<td>Endocrinology</td>
<td>Nonspecific (Homozgyous Familial Hypercholesterolemia)</td>
<td>1 INDICATIONS AND USAGE</td>
<td>REPATHA is indicated: (-) <em>As an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C</em></td>
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<td>125522, 08/06/2022</td>
<td>Evolocumab (2)</td>
<td>Endocrinology</td>
<td>Nonspecific (Homozgyous Familial Hypercholesterolemia)</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
<td>2.1 Recommended Dosage *In adults and pediatric patients aged 10 years and older with HoFH: o The initial recommended dosage of REPATHA is 420 mg once monthly administered subcutaneously [see Dosage and Administration (2.3)]. o The dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. o Patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. Administer REPATHA after the apheresis session is complete.</td>
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<tr>
<td>125522, 08/06/2022</td>
<td>Evolocumab (2)</td>
<td>Endocrinology</td>
<td>Nonspecific (Homozgyous Familial Hypercholesterolemia)</td>
<td>6 ADVERSE REACTIONS</td>
<td>Adverse Reactions in Adults and Pediatric Patients with HoFH In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH, 33 patients received 420 mg of REPATHA subcutaneously once monthly [see Clinical Studies (14)]. The mean age was 31 years (range: 13 to 68 years), 51% were women, 80% White, 12% Asian, 1% Native American, and 7% other; 5% identified as Hispanic ethnicity. No new adverse reactions were observed during the open-label extension study.</td>
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<td>125522, 08/06/2022</td>
<td>Evolocumab (2)</td>
<td>Endocrinology</td>
<td>Nonspecific (Homozgyous Familial Hypercholesterolemia)</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
<td>8.4 Pediatric Use *Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.</td>
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The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is supported by evidence from an adequate and well-controlled trial in adults and pediatric patients aged 13 years and older with HoFH (including 7 pediatric patients treated with REPATHA) and from open-label studies which included an additional 19 pediatric patients aged 11 years and older with HoFH not previously treated with REPATHA (see Adverse Reactions (6.1) and Clinical Studies (14)).

The safety and effectiveness of REPATHA have not been established in pediatric patients with HoFH or HoFH who are younger than 10 years old or in pediatric patients with other types of hyperlipidemia.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Population

Pediatric Patients

The pharmacokinetics of REPATHA were evaluated in 103 pediatric patients aged 10 to 17 years with HeFH (Study 6) (see Use in Specific Populations (8.4), Clinical Studies (14)). Following subcutaneous administration of 420 mg REPATHA once monthly, mean trough serum concentrations were 22.4 mcg/mL and 25.8 mcg/mL over the Week 12 and Week 24 time points, respectively. The pharmacokinetics of REPATHA were evaluated in 12 pediatric patients aged 11 to 17 years with HoFH (Study 9) (see Use in Specific Populations (8.4), Clinical Studies (14)). Following subcutaneous administration of 420 mg REPATHA once monthly, mean serum concentrations were 20.3 mcg/mL and 17.6 mcg/mL at Week 12 and Week 80, respectively.

14 CLINICAL STUDIES

Adults and Pediatric Patients with HoFH

Study 7 (TESLA, NCT01588496) was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with HoFH. In this trial, 33 patients received subcutaneous injections of 420 mg of REPATHA once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe). The study included 14 pediatric patients (ages 13 to 17 years). All patients in the study were initially treated with REPATHA 420 mg once monthly except for those receiving lipid apheresis at enrollment, who began with REPATHA 420 mg every 2 weeks. Dose frequencies were based on percent change from baseline LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents. (See Table 9) (…)

Study 8 (TAUSSIG, NCT01624142) was a multicenter, open-label, 5-year extension study with REPATHA in 106 patients with HoFH, who were treated with REPATHA as an adjunct to other lipid-lowering therapies. The study included 14 pediatric patients (ages 13 to 17 years). All patients in the study were initially treated with REPATHA 420 mg once monthly except for those receiving lipid apheresis at enrollment, who began with REPATHA 420 mg every 2 weeks. Dose frequencies were based on percent change from baseline LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents. (See Table 9) (…)

Study 9 (HAUSER-OLE, NCT02624869) was an open-label, single-arm, multicenter, 80-week study to evaluate the safety, tolerability, and efficacy of REPATHA for LDL-C reduction in pediatric patients aged 10 to 17 years with HoFH (see Use in Specific Populations (8.4), Clinical Studies (14)). Patients were on a low-fat diet and receiving background lipid-lowering therapy. Overall, 12 patients with HoFH received 420 mg REPATHA subcutaneously once monthly. The mean age was 12 years (range 11 to 17 years), 17% were female, 75% White, 17% Asian, and 8% Other. Median (Q1, Q3) LDL-C at baseline was 398 (343, 475) mg/dL, and all patients were on statins (atorvastatin or rosuvastatin) and ezetimibe. No patients were receiving lipid apheresis. The diagnosis of HoFH was made by genetic confirmation in all patients but enrollment by a clinical diagnosis was permitted. The median (Q1, Q3) percent change in LDL-C from baseline to Week 80 was −14% (< −41, 4). Two of the 3 subjects with < 5% LDL-C activity responded to evolocumab treatment.

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<td>761139, 11/04/2022</td>
<td>Fam-Trastuzumab Deruxtecan-nxki (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
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<td>1.1 HER2-Positive Metastatic Breast Cancer</td>
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<td>ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:</td>
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<td>• in the metastatic setting, or</td>
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<td>• in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.</td>
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<td>1.2 HER2-Low Metastatic Breast Cancer</td>
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<td>ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+ISH+) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy [see Dosage and Administration (2.1)].</td>
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<td>1.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer</td>
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|                                        | | | | | ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
|                                        | | | | | This indication is approved under accelerated approval based on objective response rate and duration of response [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. |
|                                        | | | | | 1.4 Locally Advanced or Metastatic Gastric Cancer |
|                                        | | | | | ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. |

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Unresectable or Metastatic HER2-Low Breast Cancer
Select patients for treatment of unresectable or metastatic HER2-low breast cancer with ENHERTU based on HER2 expression (IHC 1+ or IHC 2+ISH+) [see Clinical Studies (14.2)].

Unresectable or Metastatic HER2-Mutant NSCLC
Select patients for the treatment of unresectable or metastatic HER2-mutant NSCLC with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in tumor or plasma specimens [see Clinical Studies (14.3)]. If no mutation is detected in a plasma specimen, test tumor tissue.

Locally Advanced or Metastatic Gastric Cancer
Select patients with locally advanced or metastatic gastric cancer based on HER2 protein overexpression or HER2 gene amplification. Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.

Additional Patient Selection
Information on FDA-approved tests for the detection of HER2 protein expression, HER2 gene amplification, and activating HER2 mutations is available at: http://www.fda.gov/CompanionDiagnostics

5 WARNINGS AND PRECAUTIONS
5.1 Interstitial Lung Disease/Pneumonitis
Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

5.2 Neutropenia
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

5.3 Left Ventricular Dysfunction
Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see Dosage and Administration (2.3)].

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

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The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 3.6% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were 65 years or older and 8% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

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<tr>
<td>Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)</td>
<td>In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3. In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.</td>
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<tr>
<td>Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)</td>
<td>The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02664900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients, 65% were exposed for greater than 6 months and 39% were exposed for greater than one year. In this pooled safety population, the most common (20%) adverse reactions (including laboratory abnormalities) were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).</td>
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<tr>
<td>Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)</td>
<td>The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01. HER2-Positive Metastatic Breast Cancer</td>
<td>The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03 [see Clinical Studies (14.1)]. DESTINY-Breast01 and Study DS8201-A-J101 The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 [see Clinical Studies (14.1)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31). HER2-Low Metastatic Breast Cancer The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast04 [see Clinical Studies (14.2)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU. Unresectable or Metastatic HER2-Mutant NSCLC DESTINY-Lung02 evaluated two dose levels (6.4 mg/kg [N=101] and 6.4 mg/kg [N=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, includingILD/pneumonitis. Locally Advanced or Metastatic Gastric Cancer The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 [see Clinical Studies (14.4)]. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg intravenously every three weeks or either irinotecan (N=55) 150 mg/m2 biweekly or paclitaxel (N=7) 80 mg/m2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.</td>
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<tr>
<td>Locally Advanced or Metastatic Gastric Cancer</td>
<td>The administration of multiple doses of ENHERTU 6.4 mg/kg every 3 weeks did not show a large mean effect (i.e. &gt;20 ms) on the QTc interval in an open-label, single-arm study in 51 patients with metastatic HER2-positive cancer. Unresectable or Metastatic HER2-Mutant NSCLC At the recommended dosage of ENHERTU for patients with HER2-mutant NSCLC, the geometric mean (CV%) Cmax,ss of fam-trastuzumab deruxtecan-nxki and DXd were 141 µg/mL (21%) and 7.2 ng/mL (44%), respectively, and the AUCss of fam-trastuzumab deruxtecan-nxki and DXd were 775 µg·day/mL (33%).</td>
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and 40.9 ng·day/mL (43%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 31% at steady-state based on population pharmacokinetic analysis. Locally Advanced or Metastatic Gastric Cancer

At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the geometric mean Cmax,ss of fam-trastuzumab deruxtecan-nxki and DXd were 126 μg/mL (18%) and 5.2 ng/mL (42%), respectively, and the AUCss of fam-trastuzumab deruxtecan-nxki and DXd were 743 μg·day/mL (26%) and 33 ng·day/mL (43%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 39% at steady-state (Cycle 3). Elimination

The median elimination half-life (t1/2) of fam-trastuzumab deruxtecan-nxki in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately 5.4-5.7 days. Based on population pharmacokinetic analysis, the estimated systemic clearance of fam-trastuzumab deruxtecan-nxki was 0.41 L/day. The median apparent elimination half-life (t1/2) of DXd in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately 5.4-6.1 days. Based on population pharmacokinetic analysis, the estimated apparent systemic clearance of DXd was 18.3 L/h.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of ENHERTU or other anti-HER2 products.

During the median 14-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast03 with a median ADA sampling period of 13 months, treatment-emergent ADA (or anti-fam-trastuzumab deruxtecan-nxki antibodies) developed in 1.6% (4256) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0.4% (1256). During the median 7-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast01 with a median ADA sampling period of 9 months, treatment-emergent ADA developed in 2.0% (7307) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0.4% (249). During the median 8-month treatment period in HER2-low breast cancer patients in DESTINY-Breast04 with a median ADA sampling period of 8 months, treatment-emergent ADA developed in 2.0% (7037) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0357). During the median 3.5-month treatment period in HER2-mutant NSCLC patients in DESTINY-Lung02 with a median ADA sampling period of 2.2 months, treatment-emergent ADA developed in 0.7% (2490) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0249). During the median 4.6-month treatment period in HER2-positive gastric or GE adenocarcinoma patients in DESTINY-Gastric01 with a median ADA sampling period of 4.6 months, treatment-emergent ADA developed in 7.3% (9123) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0123).

Due to the limited number of patients who tested positive for ADA, the effect of treatment-emergent ADAs and treatment-emergent neutralizing antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of fam-trastuzumab deruxtecan-nxki is unknown.

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

The efficacy of ENHERTU was evaluated in study DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. (…)

DESTINY-Breast01

The efficacy of ENHERTU was evaluated in study DESTINY-Breast01 (NCT03248492), a multicenter, single-arm, trial that enrolled 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients were excluded for a history of treated ILD or current ILD at screening. Patients were also excluded for history of clinically significant cardiac disease, active brain metastases, and ECOG performance status >1. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. (…)

14.2 HER2-Low Metastatic Breast Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Breast04 (NCT03734029), a randomized, multicenter, open-label study that enrolled 557 adult patients with HER2-positive, unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor-positive (HR+) patients and 63 hormone receptor-negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined at a central laboratory using Ventana’s PATHWAY anti-HER2/neu (485) Rabbit Monoclonal Primary Antibody assay. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=373) by intravenous infusion every 3 weeks or physician’s choice of chemotherapy (N=194, eribulin, capecitabine, gemcitabine, nab-paclitaxel, or paclitaxel). Randomization was stratified by HER2 IHC status of tumor samples (IHC 1+ or IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6 treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). (…)

14.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU was evaluated in DESTINY-Lung01 (NCT03050710) and at two dose levels in DESTINY-Lung02 (NCT04644237). Patients were prospectively selected for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations by local testing using tissue. Samples from DESTINY-

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| 761139, 11/04/2022 | Fam-Trastuzumab Deruxtecan-mxki (2) | Oncology | ESR (Hormone Receptor) | Lung01 were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation, Tissue-test) and Guardant360® CDx test (Guardant Health Inc., Plasma test). (…) The efficacy of ENHERTU was evaluated in DESTINY-Lung02, a multicenter, multi-cohort, randomized, blinded, dose-optimization trial. Eligible patients were required to have unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after one prior systemic therapy. Patients with a history of steroid dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and EOCG performance status >1 were excluded. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with stable brain metastases at baseline. Results from an interim efficacy analysis in a pre-specified patient cohort are described below. The major efficacy outcomes were confirmed ORR as assessed by BICR using RECIST v1.1 and DOR. The median age was 58 years (range 30 to 78); 69% were female; 79% were Asian, 12% were White, and 10% were other races; 29% had an EOCG performance status of 0; 71% had 1; 33% had stable brain metastases; 94% had a mutation in the ERBB2 kinase domain and 6% had a mutation in the extracellular domain. The median number of prior regimens was 2 (range: 1 to 12); 100% of patients received prior platinum therapy, 71% received prior immunotherapy, and 44% received both in combination. Fifty percent of patients were never-smokers and 50% were former smokers; 96% of patients had adenocarcinoma histology. 14.4 Locally Advanced or Metastatic Gastric Cancer The efficacy of ENHERTU was evaluated in study DESTINY-Gastric01 (NCT03329969), a multicenter, open-label, randomized trial conducted in Japan and South Korea that enrolled 188 adult patients with HER2-positive (IHC 3+ or IHC 2+ISH positive), locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. HER2 expression was determined by a central lab on tissue obtained either before or after prior trastuzumab treatment. Patients were excluded for a history of treated or current ILD, a history of clinically significant cardiac disease, active brain metastases, or EOCG performance status >1. Patients were randomized 2:1 to receive ENHERTU (N=126) 6.4 mg/kg intravenously every 3 weeks or physician’s choice of chemotherapy: irinotecan monotherapy (N=50), 150 mg/m2 intravenously every 2 weeks or paclitaxel monotherapy (N=17) 80 mg/m2 intravenously weekly. Randomization was stratified by HER2 status (IHC 3+ or IHC 2+ISH+), EOCG performance status (0 or 1), and region (Japan or South Korea). Tumor imaging assessments were performed at screening and every 6 weeks from the first treatment dose. Treatment was administered until unacceptable toxicity or disease progression. The major efficacy outcomes were ORR assessed by ICR according to RECIST v1.1 and OS in the intent-to-treat population. Additional efficacy outcomes were PFS and DOR. The median age was 66 years (range 28 to 82); 76% were male; and 100% were Asian. All patients received a trastuzumab product. Patients had an EOCG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+ISH+; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; 45% had three or more prior regimens in the locally advanced or metastatic setting. A total of 30% of patients were identified as HER2-positive using tissue obtained following prior treatment with a trastuzumab product. 14.1 HER2-Positive Metastatic Breast Cancer DESTINY-Breast01 (…) The median age was 54 years (range: 20-83); 80% were <65 years and 99.6% were female. The majority of patients were Asian (60%), White (27%) and Black (3%). Seven percent (7%) of patients were of Hispanic/Latino ethnicity. Patients had an EOCG performance status of 0 (63%) or 1 (37%) at baseline. Seventy-three percent had visceral disease, 16% had brain metastases at baseline, 52% were hormone receptor positive (HR+) and 48% of patients had received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 10%. DESTINY-Breast01 The median age was 55 years (range: 28-96); 76% of patients were <65 years. All 184 patients were female, and the majority were White (55%) or Asian (38%). Patients had an EOCG performance status of 0 (55%) or 1 (44%) at baseline. Ninety-two percent had visceral disease, 29% had bone metastases, and 13% had brain metastases. Fifty-three percent were HR+. Sum of diameters of target lesions were <5 cm in 42%, and ≥5 cm in 50% (not evaluable by central review in 8% of patients). 14.2 HER2-Low Metastatic Breast Cancer The efficacy of ENHERTU was evaluated in study DESTINY-Breast04 (NCT03734029), a randomized, multicenter, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 484 hormone receptor-positive (HR+) patients and 63 hormone receptor-negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+ISH-, as determined at a central laboratory using Ventana’s PATHWAY anti-HER-2/nue antibody (4B5) Rabbit Monoclonal Primary Antibody assay. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=373) by intravenous infusion every 3 weeks or physician's choice of chemotherapy (N=184, eribulin, capecitabine, gemcitabine, nab paclitaxel, or paclitaxel). Randomization was stratified by HER2 IHC status of tumor samples (IHC 1+ or IHC 2+ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and status/prior CDK4/6 inhibitor treatment. HR+ without prior CDK4/6 inhibitor treatment, or HR- (…). The major efficacy outcome measure was PFS by BICR based on RECIST v1.1. Additional efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomized HR+ and HR- patients), OS in HR+ patients, and OS in the overall population. The median age was 57 years (range: 28 to 81); 24% were age 65 or older; 99.6% were female; 48% were White, 40% were Asian, and 2% were Black or African American; 3% of patients were Hispanic/Latino ethnicity. Patients had an EOCG performance status of 0 (55%) or 1 (45%) at baseline; 58% were IHC 1+, 42% were IHC 2+ISH-, 70% had liver metastases, 33% had lung metastases, and 6% had brain metastases. In the metastatic setting, patients had a

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<td>Fesoterodine</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.2 CYP2A4 Inhibitors Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP2A4 inhibitors, such as ketoconazole, itraconazole, and clindamycin. Co-administration of the potent CYP2A4 inhibitor ketoconazole with fesoterodine led to an approximately doubling of the maximum concentration (Cmax) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl toremifene (5-HMT), the active metabolite of fesoterodine. Compared with CYP2D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole [see Clinical Pharmacology (12.3), Warnings and Precautions (5.8), and Dosage and Administration (2.1)]. 7.4 CYP2D6 Inhibitors The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. No dosage adjustments are recommended in the presence of CYP2D6 inhibitors.</td>
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<tr>
<td>Flibanserin 022526, 08/18/2015</td>
<td>Flibanserin (1)</td>
<td>Gynecology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12.2 Pharmacodynamics Cardiac Electrophysiology (…) Electrocardiographic parameters were measured over a 24-hour period at pre-dose, after the first administration, and after the third administration of study medication. Flibanserin 28 mg was chosen because this dose, when administered to CYP2D6 extensive metabolizers, results in an exposure to the active metabolite that is similar to the exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg together with CYP3A4 blockade. (…) 12.3 Pharmacokinetics Metabolism (…) A summary of pharmacokinetic parameters for the active metabolite after a single dose of Toviaz 4 mg and 8 mg in extensive and poor metabolizers of CYP2D6 is provided in Table 2. (See Table 8) (…) Absorption (…) Variability in CYP2D6 Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6. Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 poor metabolizers, as compared to extensive metabolizers. Pediatric Patients: In pediatric patients, from 6 years to 17 years of age with NDO weighing 35 kg with CYP2D6 extensive metabolizer status receiving Toviaz tablets, the mean values of distribution and absorption constant, volume of distribution and absorption constant, and clearance of fesoterodine were 72 L/h, 70 L and 0.69 h⁻¹, respectively. The Tmax and half-life of 5-HMT are estimated to be approximately 2.55 h and 7.73 h, respectively. Like adults, the 5-HMT exposures in CYP2D6 poor metabolizers was estimated to be approximately 2-fold higher compared with extensive metabolizers. The post-hoc estimates of steady-state exposures of 5-HMT in NOO patients weighing greater than 25 kg following Toviaz 4 mg and 8 mg tablets once daily are summarized in Table 9. Drug-Drug Interactions CYP2A4 Inhibitors: Following co-administration of the potent CYP2A4 inhibitor ketoconazole 200 mg twice a day for 5 days, Cmax and AUC of the active metabolite of fesoterodine increased 2.0- and 2.3-fold, respectively, after oral administration of Toviaz 8 mg to CYP2D6 extensive metabolizers. In CYP2D6 poor metabolizers, Cmax and AUC of the active metabolite of fesoterodine increased 2.1- and 2.5-fold, respectively, during co-administration of ketoconazole 400 mg twice a day for 5 days. Cmax and AUC were 4.5- and 5.7-fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. In separate study co-administering fesoterodine with ketoconazole 200 mg once a day for 5 days, the Cmax and AUC values of the active metabolite of fesoterodine were increased 2.2- and 2.6-fold in CYP2D6 extensive metabolizers and 3.4- and 4.2-fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. There is no clinically relevant effect of moderate CYP3A4 inhibitors on the pharmacokinetics of fesoterodine. (…) CYP2D6 Inhibitors: The interaction with CYP2D6 inhibitors was not studied. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. [see Drug Interactions (7.4)].</td>
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| Flibanserin 022526, 08/18/2015         | Flibanserin (2) | Gynecology | CYP2C19 | Adverse Reactions, Use in Specific Populations | 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Syncope in Poor CYP2C19 Metabolizers In a pharmacogenomic study of 100 mg ADDYI in subjects who were poor or extensive CYP2C19 metabolizers, syncope occurred in 1/9 (11%) subjects who were CYP2C19 poor metabolizers (this subject had a 3.2 fold higher fribanserin exposure compared to CYP2C19 extensive metabolizers) compared to no such occurrence in extensive metabolizers. * Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.
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<td>Clinical Pharmacology</td>
<td>adverse reactions in subjects who were CYP2C19 extensive metabolizers [see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)].</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.7 CYP2C19 Poor Metabolizers</td>
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<td>CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer [see Adverse Reactions (6.1) and Clinical Pharmacology (12.5)]. Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.</td>
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<td>12.5 Pharmacogenomics</td>
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<td>Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes.</td>
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<td>CYP2C19 Poor Metabolizers</td>
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<td>A study comparing flibanserin exposure in CYP2C19 poor metabolizers to CYP2C19 extensive metabolizers was conducted in lieu of a drug interaction study with ABDV1 and a strong CYP2C19 inhibitor. In 9 women who were poor metabolizers of CYP2C19, Cmax and AUC0-inf of flibanserin 100 mg once daily increased 1.5-fold (1.1-2.1) and 1.3-fold (0.9-2.1), compared to exposures among 8 extensive metabolizers of CYP2C19. Flibanserin half-life was increased from 11.1 hours in the extensive metabolizers of CYP2C19 to 13.5 hours in the poor metabolizers of CYP2C19 [see Adverse Reactions (6.1) and Use in Specific Populations (8.7)]. The frequencies of poor metabolizers of CYP2C19 are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.</td>
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<td>Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes.</td>
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<td>A study comparing flibanserin exposure in CYP2D6 extensive metabolizers to CYP2D6 extensive metabolizers was conducted in addition to a drug interaction study with paroxetine, a strong CYP2D6 inhibitor. In 12 poor metabolizers of CYP2D6, steady state Cmax and AUC of flibanserin 50 mg twice daily was decreased by 4% and increased by 18%, respectively, compared to exposures among 19 extensive metabolizers, intermediate metabolizers and ultra rapid metabolizers of CYP2D6.</td>
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<td>CONTRAINDICATIONS</td>
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<td>(…) Carac should not be used in patients with dihydouracilid methyltransferase (DPT) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydouracilid methyltransferase (DPT). DPT enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. (…)</td>
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<td>The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive. Patients should discontinue therapy with Carac if symptoms of DPT enzyme deficiency develop. Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parental administration of fluorouracil has been attributed to deficiency of dihydouracilid methyltransferase “DPT” activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPT enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPT enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil. Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase (DPD) Activity</td>
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<td>Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Withheld or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.</td>
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<td>Fluoxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS 5.11 QT Prolongation Post-marketing cases of QT interval prolongation and ventricular arrhythmia including torsades de pointes have been reported in patients treated with PROZAC. PROZAC should be used with caution in patients with congenital long QT syndrome; a previous history of QT prolongation; a family history of long QT syndrome or sudden cardiac death; and other conditions that predispose to QT prolongation and ventricular arrhythmia. Such conditions include concomitant use of drugs that prolong the QT interval; hypokalemia or hypomagnesemia; recent myocardial infarction, uncompensated heart failure, bradyarrhythmias, and other significant arrhythmias; and conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs). PROZAC is primarily metabolized by CYP2D6 [see Contraindications (4.2), Adverse Reactions (6.2), Drug Interactions (7.7, 7.8), Overdosage (10.1), and Clinical Pharmacology (12.3)].</td>
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<td>018766, 05/09/2016</td>
<td>Flurbiprofen</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Variability in Metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled ranitidine, differences in the rate and extent of absorption and bioavailability were observed. These differences were more pronounced in poor metabolizers. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs, antipsychotics (e.g., phenothiazines and most atypicals), and antihistamines (e.g., propafenone, felodipine, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks.</td>
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<tr>
<td>018554, 07/23/2001</td>
<td>Fluoxetine</td>
<td>Oncology</td>
<td>G6PD</td>
<td>WARNINGS Aniline Toxicity: One metabolite of flutamide is 4-nitro-3-fluoromethylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia and cholestatic jaundice, have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (i.e., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methemoglobin levels should be considered.</td>
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<tr>
<td>02007, 05/29/2019</td>
<td>Formoterol (1)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.</td>
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<td>02007, 05/29/2019</td>
<td>Formoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2C19</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.</td>
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<tr>
<td>02/26/2021, 214018</td>
<td>Fosdenopterin</td>
<td>Neurology</td>
<td>MOC5</td>
<td>1 INDICATIONS AND USAGE NULIBRY is indicated to reduce the risk of mortality in patients with myelodyodenal colactor deficiency (MoCD) Type A.</td>
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<td></td>
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<td>Clinical Pharmacology, Clinical Studies</td>
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6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Overview of Safety Evaluation
The safety of NULIBRY was assessed in 37 pediatric patients and healthy adults who received at least one intravenous infusion of NULIBRY or an E. coli derived non-salt, anhydrous form of cPMP (recombinant cPMP or rcPMP, which has the same active moiety and therefore the same biologic activity as NULIBRY). Of these 37 patients/healthy adults, 13 were pediatric patients with MoCD Type A in Studies 1, 2, and 3 (see Clinical Studies (14)), 6 were pediatric patients with presumptive MoCD Type A but who were later confirmed to have neither MoCD Type A, and 18 were healthy adults (without MoCD Type A) in a Phase 1 study.

Adverse Reactions
Assessment of adverse reactions for NULIBRY is based on data from two open-label, single-arm studies, Study 1 (n=8) and Study 2 (n=1), in patients with a confirmed diagnosis of MoCD Type A (8 of the 9 patients were previously treated with rcPMP). In these studies, patients received a daily intravenous infusion of NULIBRY. The median exposure to NULIBRY was 43.5 years and ranged from 8 days to 5.8 years [see Clinical Studies (14)]. In these studies, 44% of patients were males and 56% were females, 67% were White and 33% were Asian. The median age was 14 years and ranged from 1 day to 69 days at time of first infusion.

Table 2 presents the most common adverse reactions that occurred in NULIBRY-treated patients in Studies 1 and 2. (See Table 2)

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
Safety and effectiveness of NULIBRY for the treatment of MoCD Type A have been established in pediatric patients starting from birth. Use of NULIBRY for this indication is supported by evidence from two open-label studies (Studies 1 and 2) and one observational study (Study 3), in which 13 pediatric patients aged birth to 6 years of age were treated with NULIBRY or rcPMP. Pediatric use information is discussed throughout the labeling.

8.5 Geriatric Use
MoCD Type A is largely a disease of pediatric patients. Clinical studies of NULIBRY did not include patients 65 years of age and older.

8.6 Adult Use
The safety and effectiveness of NULIBRY for the treatment of adults with MoCD Type A have been established. Use of NULIBRY in adults for this indication is based on an adequate and well-controlled clinical investigation in pediatric patients [see Clinical Studies (14)].

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
In MoCD Type A, the lack of effective SOX leads to elevated levels of the neurotoxic sulfite, S-sulfocysteine (SSC). Treatment with NULIBRY resulted in a reduction in the level of urinary SSC normalized to creatinine and the reduction was sustained with long-term treatment with NULIBRY [see Clinical Studies (14)].

Specific Populations
Pediatric Patients
Pharmacokinetic properties of fosdenopterin in pediatric MoCD Type A patients are similar to healthy adult subjects.

14 CLINICAL STUDIES
The efficacy of NULIBRY for the treatment of patients with MoCD Type A was established based on data from three clinical studies (Studies 1, 2, and 3) that were compared to data from a natural history study.

Study 1 (NCT002047461) was a prospective, open-label, single-arm, dose escalation study in patients with MoCD Type A who were receiving treatment with rcPMP prior to treatment with NULIBRY. Study 1 included 8 patients, 6 of whom previously participated in Study 3. The initial NULIBRY dosage was matched to the patient’s rcPMP dosage upon entering the study. The NULIBRY dosage was then titrated over a period of 5 months to a maximum dosage of 0.9 mg/kg administered once daily as an intravenous infusion.

Study 2 (NCT00829393) was a prospective, open-label, single-arm, dose escalation study in one patient with MoCD Type A who had not been previously treated with rcPMP. The initial dosage of NULIBRY in Study 2 was based on the gestational age of the patient (i.e., 36 weeks). The initial dosage was then incrementally escalated up to a maximum dosage of 0.98 mg/kg administered once daily as an intravenous infusion (1.1 times the maximum approved recommended dosage) [see Dosage and Administration (2.1)].

Study 3 was a retrospective, observational study that included 10 patients with a confirmed diagnosis of MoCD Type A who received rcPMP. Six of these 10 patients were later enrolled in Study 1 to receive treatment with NULIBRY. Efficacy Results The efficacy of NULIBRY and rcPMP were assessed in a combined analysis of the 13 patients who genetically confirmed MoCD Type A from Study 1 (n=8), Study 2 (n=1), and Study 3 (n=4) who received substrate replacement therapy with NULIBRY or rcPMP. Of the 13 treated patients included in the combined analysis, 54% were male, 77% were White and 23% were Asian; the median gestational age was 39 weeks (range 35 to 41 weeks). Of these 13 treated patients, the age at first dose was ≤ 14 days for 10 patients (with 5 patients initiating treatment at 1 day of age) and ≤ 32 days and < 69 days for the remaining 3 patients. Overall Survival Efficacy was assessed by comparing overall survival in pediatric patients treated with NULIBRY or rcPMP (n=13) with an untreated natural history cohort of pediatric patients with genetically confirmed MoCD Type A.
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| 020450, 02/16/2021                   | Fosphenytoin (1) | Neurology | CYP2C9 | Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS

5.4 Serious Dermatologic Reactions

CEREBYX can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin (the active metabolite of CEREBYX)-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.5)]. The onset of symptoms is usually within 28 days, but can occur later. CEREBYX should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding CEREBYX as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers.

Should CEREBYX be utilized for CYP2C9*3 carriers, consider starting at the lower end of the dosage range [see Use in Specific Populations (8.7)].

The prevalence of the CYP2C9 variant is approximately 2-3% in the White population, 0.5-4% in the Asian population, and <1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-30% in the Asian population [see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)].

5.4 Warnings and Precautions

5.4.1 Use in Patients with Decreased CYP2C9 Function

Patients who are intermediate or poor metabolizers of CYP2C9 substrates (e.g., *1/*3, *2/*2, *3/*3) may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers (e.g., *1/*1). Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses to maintain similar steady-state concentrations compared to normal metabolizers. In patients who are known to be carriers of the decreased function CYP2C9*2 or *3 alleles (intermediate and poor metabolizers), consider starting at the low end of the dosage range and monitor serum concentrations to maintain total phenytoin concentrations of 10 to 20 mcg/mL. If early signs of dose-related central nervous system (CNS) toxicity develop, serum concentrations should be checked immediately [see Clinical Pharmacology (12.5)].

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate (e.g., *1/*3, *2/*2) or poor metabolism (e.g., *2/*3, *3/*3) have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also result in decreased clearance of phenytoin (e.g., *5, *6, *8, *11).

The prevalence of the CYP2C9 polymorphism ranges from 2-3% in the White population, 0.5-4% in the Asian population, and <1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-30% in the Asian population [see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)].
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<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS</td>
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<td></td>
<td>7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes</td>
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|                                        |       |                |                  |                  | (…).
|                                        |       |                |                  |                  | Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as “poor metabolizers” (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an in vivo study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated reduced pharmacokinetic properties compared to 16 “extensive metabolizers” (EM): mean Cmax, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patient known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isozyme (e.g., quinidine). |
| 217564, 11/08/2023                     | Fruquintinib | Oncology | RAS | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE |
|                                        |       |                |                  |                  | FRUZAQLA is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy. |
| 021344, 05/13/2020                     | Fulvestrant (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE |
|                                        |       |                |                  |                  | Monotherapy |
|                                        |       |                |                  |                  | FASLODEX is indicated for the treatment of: |
|                                        |       |                |                  |                  | - Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or |
|                                        |       |                |                  |                  | - HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. |
|                                        |       |                |                  |                  | Combination Therapy |
|                                        |       |                |                  |                  | FASLODEX is indicated for the treatment of: |
|                                        |       |                |                  |                  | - HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy. |
|                                        |       |                |                  |                  | - HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy. |
|                                        |       |                |                  |                  | 6 ADVERSE REACTIONS |
|                                        |       |                |                  |                  | 6.1 Clinical Trials Experience |
|                                        |       |                |                  |                  | Combination Therapy with Palbociclib (PALOMA-3) |
|                                        |       |                |                  |                  | The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months. (…). |

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| 021344, 05/13/2020                      | Fulvestrant (2) | Oncology | ESR, PGR (Hormone Receptor) | 1 INDICATIONS AND USAGE | Monotherapy: FASLODEX is indicated for the treatment of:  
- Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women who have not previously been treated with endocrine therapy.  
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.  
Combination Therapy: FASLODEX is indicated for the treatment of:  
- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy.  
- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.  

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Comparison of FASLODEX 500 mg and Anastrozole 1 mg (FALCON)  
The safety of FASLODEX 500 mg versus anastrozole 1 mg was evaluated in FALCON. The data described below reflect exposure to FASLODEX in 228 out of 460 patients with HR-positive advanced breast cancer in postmenopausal women not previously treated with endocrine therapy who received at least one (1) dose of treatment in FALCON. (…)  
Combination Therapy with Palbociclib (PALOMA-3)  
The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 378 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least one dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo was 9.7 months. (…)  
Combination Therapy with Abemaciclib (MONARCH 2)  
The safety of FASLODEX 500 mg plus abemaciclib (150 mg twice daily) versus FASLODEX plus placebo was evaluated in MONARCH 2. The data described below reflect exposure to FASLODEX in 664 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (…) |

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| 214801, 09/30/2022 | Futibatinib | Oncology | FGF2 | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | Combination Therapy with Ribociclib (MONALEESA-3) The safety of FASLODEX 500 mg plus ribociclib 600 mg versus FASLODEX plus placebo was evaluated in MONALEESA-3. The data described below reflect exposure to FASLODEX plus ribociclib in 483 out of 724 postmenopausal women with hormone receptor positive, HER2-negative metastatic breast cancer who had received no or only one line of prior endocrine therapy. (…)

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the ER pathway were also decreased in Ki67 labeling index, a marker of cell proliferation.

14 CLINICAL STUDIES
Combination Therapy
Patients with hormone receptor positive, HER2-negative advanced or metastatic breast cancer who had received no or only one line of prior adjuvant or metastatic endocrine therapy
FASLODEX 500 mg in Combination with Palbociclib 125 mg (PALOMA-3)
PALOMA-3 (NCT-1942135) was an international, randomized,-double-blind, parallel group, multi-center study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with hormone receptor positive, HER2-negative advanced or metastatic breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…)
FASLODEX 500 mg in Combination with Abraxol 150 mg (MONARCH 2)
MONARCH 2 (NCT02170703) was a randomized, placebo-controlled, multi-center study conducted in women with hormone receptor positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy treated with FASLODEX plus abraxol versus FASLODEX plus placebo. (…)
Postmenopausal women with HER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy
FASLODEX 500 mg in Combination with Ribociclib 600 mg (MONALEESA-3)
MONALEESA-3 (NCT-02422915) was a randomized, double-blind, placebo-controlled study of FASLODEX plus ribociclib versus FASLODEX plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)

LYTGOBI is indicated for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements [see Dosage and Administration (2.1)].

12.2.1 Dose in Combination with Ribociclib
LYTGOBI is administered orally at a dosage of 20 mg once daily until disease progression or unacceptable toxicity. The median duration of treatment was 9 months (range: 0.5 - 25 months). (…)

6 ADVERSE REACTIONS
Previously Treated, Unresectable Locally Advanced or Metastatic Intrahepatic Cholangiocarcinoma
The safety of LYTGOBI was evaluated in Study TAS-120-101, which included 103 patients with previously treated, unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 fusions or other gene rearrangements [see Clinical Studies (14.1)]. Patients were treated with LYTGOBI 20 mg orally once daily until disease progression or unacceptable toxicity. The median duration of treatment was 9 months (range: 0.5 - 25 months). (…)

14 CLINICAL STUDIES
14.1 Cholangiocarcinoma
TAS-120-101 (NCT02052778), a multicenter, open-label, single-arm trial, evaluated the efficacy of LYTGOBI in 103 patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma. The presence of FGFR2 fusions or other rearrangements was determined in 102 enrolled patients (96%) using next generation sequencing (NGS) testing. Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene leaving the FGFR2 kinase domain intact. Patients received LYTGOBI at a dosage of 20 mg orally once daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) as determined by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The trial population characteristics were: Median age was 58 years (range: 22 to 79 years) with 22% of patients ≥65 years, 56% were male, race was: 50% White, 29% Asian, 8% Black or African American, 1% Native Hawaiian or Other Pacific Islander, 13% unknown, baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (47%) or 1 (53%). Seventy-eight percent (78%) of patients had in-frame FGFR2 gene fusions and the most commonly identified FGFR2 fusion partner was BICC1 (n=24, 23%). Twenty-two percent (22%) of patients had other FGFR2 rearrangements that may not be in-frame with the partner gene or the partner gene was not identifiable. (…)

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| 021169, 02/14/2017                    | Galantamine | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isozymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly. O-demethylation, mediated by CYP2D6, was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In studies of oral 3H-galantamin, unchanged galantamine and its glucuronide, accounted for most total radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-96% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average. (…) RAZADYNE® ER 24 mg extended-release capsules administered once daily under fasting conditions are bioequivalent to RAZADYNE® tablets 12 mg twice daily with respect to AUC(90h) and Cmax. The Cmax and Tmax of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with Cmax about 25% lower and median Tmax occurring about 4.5–5.0 hours after dosing. Dose-proportionally is observed for RAZADYNE® ER extended-release capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER extended-release capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. (…) CYP2D6 Poor Metabolizers Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% increase in Cmax and about 35% lower with respect to AUC(90h) and Cmax. The Cmax and Tmax of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with Cmax about 25% lower and median Tmax occurring about 4.5–5.0 hours after dosing. Dose-proportionally is observed for RAZADYNE® ER extended-release capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER extended-release capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. (…)

| 215804, 03/18/2022 | Ganaxolone | Neurology | CDKL5 | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE ZTALMY is indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. 14 CLINICAL STUDIES The effectiveness of ZTALMY for the treatment of seizures associated with CDD in patients 2 years of age and older was established in a single, double-blind, randomized, placebo-controlled study in patients 2 to 19 years of age (Study 1, NCT03572933).
Patients enrolled in Study 1 (N=50 for ZTALMY; N=51 for placebo) had molecular confirmation of a pathogenic or likely pathogenic mutation in the CDKL5 gene, seizures inadequately controlled by at least 2 previous treatment regimens, and a minimum of 16 major motor seizures (i.e., bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, focal to bilateral tonic-clonic) per 28 days during a retrospective 2-month period prior to screening.

| 062196 | Gemtacimcin | Infectious Diseases | MT-RNR1 | Warnings | Labeling not electronically available on Drugs@FDA

| 206995, 08/22/2018 | Gefitinib (1) | Oncology | EGFR | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations [see Clinical Studies (14)]. Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations [see Clinical Studies (14)]. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the first-line treatment of metastatic NSCLC with IRESSA based on the presence of EGFR exon 19 deletion or exon 21 (L858R) substitution mutations in their tumor [see Indications and Usage (1), Clinical Studies (14)]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnosics. 14 CLINICAL STUDIES Non-Small Cell Lung Cancer (NSCLC) Study 1 The efficacy and safety of IRESSA for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or L858R substitution mutations was demonstrated in a multicenter, single-arm, open-label clinical study (Study 1). A total of 108 treatment-naive patients with metastatic EGFR mutation positive NSCLC received IRESSA at a dose of 250 mg once daily until disease progression or intolerable toxicity. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by both a Blinded Independent Central Review (BICR) and investigators. Duration of response (DOR) was an additional outcome measure. Eligible patients were required to have a deletion in EGFR exon 19 or L858R, L856I, or Q719X substitution mutations and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. Tumor samples from 87 patients were tested retrospectively using the heracscan® EGFR RQ PCR Kit.

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
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<tbody>
<tr>
<td>206995, 08/22/2018</td>
<td>Gefitinib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
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<td>The study population characteristics were: median age 65 years, age 75 years or older (25%), age less than 65 years (49%), white (100%), female (71%), never smokers (64%), WHO PS 0 (45%), WHO PS 1 (48%), WHO PS 2 (7%), and adenocarcinoma histology (97%). Sixty patients had exon 19 deletions (65%), 29 patients had L858R substitution (31%), while two patients each had tumors harboring L861Q or G719X substitution mutation. The median duration of treatment was 8.0 months. (See Table 3) The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation with duration of response of at least 2.8 months and 5.6 months, respectively. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response with duration of response of at least 2.8 months. Study 2 The results of Study 1 were supported by an exploratory analysis of a subset of a randomized, multicenter, open-label trial (Study 2) conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients were randomized (1:1) to receive IRESSA 250 mg orally once daily or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and objective response rate (ORR) as assessed by BICR. The subset population consisted of 186 of 1217 patients (15%) determined to be EGFR positive by the same clinical trial assay as used in Study 1 and had radiographic scans available for a retrospective assessment by BICR. In this subset, there were 88 IRESSA-treated patients and 98 carboplatin/paclitaxel-treated patients. (…)</td>
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<tr>
<td>761060, 06/16/2020</td>
<td>Gemtuzumab Ozogamicin</td>
<td>Oncology</td>
<td>CD33</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
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<td>1 INDICATIONS AND USAGE 1.1 Newly-Diagnosed CD33-positive Acute Myeloid Leukemia (AML) MYLOTARG is indicated for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults and pediatric patients 1 month and older. 1.2 Relapsed or Refractory CD33-positive AML MYLOTARG is indicated for the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and pediatric patients 2 years and older. 2 DOSAGE AND ADMINISTRATION 2.2 Recommended Dosage Newly-Diagnosed De Novo CD33-positive AML (Combination Regimen) Adults The recommended dose of MYLOTARG in adults is 3 mg/m2. A treatment course including MYLOTARG in combination therapy for adults with newly-diagnosed de novo CD33-positive AML consists of 1 induction cycle and 2 consolidation cycles [see Clinical Studies (14.1)]. (…) Newly-Diagnosed CD33-positive AML (Single-agent Regimen) A treatment course of MYLOTARG as a single agent for adults with newly-diagnosed CD33-positive AML consists of 1 cycle of induction and up to 8 cycles of continuation therapy [see Clinical Studies (14.1)]. (…) Relapsed or Refractory CD33-positive AML (Single-agent Regimen) The recommended dose of MYLOTARG as a single agent for treatment for adults and pediatric patients 2 years and older with relapsed or refractory CD33-positive AML is 3 mg/m2 (up to one 4.5 mg vial) on Days 1, 4, and 7. Treatment in the relapsed or refractory setting consists of a single course of MYLOTARG [see Clinical Studies (14.2)]. (…) 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Combination Therapy in Newly-Diagnosed De Novo CD33-positive AML The safety of MYLOTARG in first-line combination therapy was evaluated in two prospective clinical trials, Study ALFA-0701 in adults and Study AAML0531 in pediatric patients. (…) Monotherapy for Newly-Diagnosed CD33-positive AML The safety evaluation of MYLOTARG (8 mg/m2 then 3 mg/m2 with 7 days between the doses) as monotherapy is based on a randomized, open-label, Phase 3 trial of MYLOTARG (N=118) versus best supportive care (BSC) (N=119) in patients with previously untreated AML who were considered ineligible for intensive chemotherapy in Study AML-19 [see Clinical Studies (14.1)]. (…) Monotherapy for Relapsed or Refractory CD33-positive AML</td>
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</table>

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<th>Labeling Text‡</th>
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<td>211349, 05/29/2019</td>
<td>Gilteritinib</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.1 Relapsed or Refractory Acute Myeloid Leukemia</td>
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<td>XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.</td>
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<td>212194, 11/20/2019</td>
<td>Givosiran</td>
<td>Gastroenterology</td>
<td>CPOX, HMBS, PPOX (Acute Hepatic Porphyria)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Newly-Diagnosed CD33-positive AML</td>
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<td>Study ALFA-0701</td>
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<td>(…) CD33 expression on AML blasts by flow cytometry harmonized from local laboratory results was determined in 194/271 (72%) patients overall. Few patients (14%) had low CD33 expression (less than 30% of blasts), and none had no expression of CD33. (…) Study AML-19</td>
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<td>(…) Patients were randomized 1:1 and stratified by age (61-75 vs 76-80 years vs ≥81 years), CD33 positivity of bone marrow blasts (less than 20 % vs 20-80% vs greater than 80% vs unknown), initial white blood cell count (less than 30 vs greater than or equal to 30 x 10⁹ /L), WHO PS (0-1 vs 2 vs 3-4), and institution. (…) Fewer patients on the MYLOTARG arm had missing cytogenetics data (22% vs 35%). CD33 expression on AML blasts by flow cytometry at a centralized location was determined in 238/237 (99%) patients; 10% had CD33 expression less than 20%. (…)</td>
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<tr>
<td>020496, 12/21/2018</td>
<td>Glimepiride</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.3 Hemolytic Anemia</td>
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<td>Sulfonlureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonlurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonlurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving AMARYL who did not have known G6PD deficiency [see Adverse Reactions (6.2)].</td>
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<td>017783, 08/18/2016</td>
<td>Glipizide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>Hemolytic Anemia</td>
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<th>Labeling Text‡</th>
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</thead>
</table>
| 020051, 08/22/2017                     | Glyburide | Endocrinology | G6PD | Precautions | PRECAUTIONS  
Hemolytic Anemia  
Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonfonylurea agents can lead to hemolytic anemia. Because GLUCOTROL belongs to the class of sulfonfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonfonylurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.  

| 203284, 09/03/2021                     | Glycerol phenylbutyrate (1) | Inborn Errors of Metabolism | ASS1, CPS1, OTC (Urea Cycle Disorders) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).  
Limitations of Use:  
• RAVICTI is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.  

| 203284, 09/03/2021                     | Glycerol phenylbutyrate (2) | Inborn Errors of Metabolism | NAGS | Indications and Usage | 1 INDICATIONS AND USAGE  
Limitations of Use:  
• The safety and efficacy of RAVICTI for the treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.  

| 211970, 12/12/2019                     | Golodirsen | Neurology | DMD | Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
VYONDYS 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53 [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.  

| 211970, 12/12/2019                     | Golodirsen | Neurology | DMD | Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
VYONDYS 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping, including pediatric patients [see Clinical Studies (14)].  

| 211970, 12/12/2019                     | Golodirsen | Neurology | DMD | Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
After treatment with VYONDYS 53, all patients evaluated (n=25) in Study 1 Part 2 [see Clinical Studies (14)] had an increase in skipping of exon 53 demonstrated by reverse transcription polymerase chain reaction (RT-PCR), compared to baseline.  

| 211970, 12/12/2019                     | Golodirsen | Neurology | DMD | Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 14 CLINICAL STUDIES  
The effect of VYONDYS 53 on dystrophin production was evaluated in one study in DMD patients with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping (Study 1; NCT02310906).  

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<td>Goserein</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.5 Advanced Breast Cancer</td>
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<td>ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.</td>
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<td>The estrogen and progesterone receptor values may help to predict whether ZOLADEX therapy is likely to be beneficial [see Dosage and Administration (2.6), Clinical Pharmacology (12.1), and Clinical Studies (14.5)].</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.5 Breast Cancer</td>
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<td>The Southwest Oncology Group conducted a prospective, randomized clinical trial (SWOG-8692 [INT-0075]) in premenopausal women with advanced estrogen receptor positive or progesterone receptor positive breast cancer which compared ZOLADEX with cyclophosphamide.</td>
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<td>(…) Findings were similar in uncontrolled clinical trials involving patients with hormone receptor positive and negative breast cancers. Premenopausal women with estrogen receptor (ER) status of positive, negative, or unknown participated in the uncontrolled (Phase II and Trial 2002) clinical trials. Objective tumor responses were seen regardless of ER status, as shown in the following table. (See Table 6)</td>
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<td>020727, 03/12/2019</td>
<td>Hydralazine</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Absorption</td>
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<td>(…) Hydralazine hydrochloride. About 2/3 of a 50-mg dose of 14C-hydralazine hydrochloride given in gelatin capsules was absorbed in hypertensive subjects. In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to 26%, with the higher percentages in slow acetylators. Administration of doses escalating from 75 mg to 1000 mg three times daily to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-linear kinetics of hydralazine, probably reflecting saturable first pass metabolism. (…)</td>
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<td>Metabolism</td>
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<td>Hydralazine is metabolized by acetylation, ring oxidation and conjugation with endogenous compounds including pyruvic acid. Acetylation occurs predominantly during the first-pass after oral administration which explains the dependence of the absolute bioavailability on the acetylator phenotype. About 50% of patients are fast acetylators and have lower exposure. (…)</td>
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<td>009768, 05/03/2021</td>
<td>Hydroxychloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.6 Hemolytic Anemia Associated with G6PD Deficiency</td>
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<td>Hemolysis has been reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor for hemolytic anemia as this can occur, particularly in association with other drugs that cause hemolysis.</td>
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<td>ADVERSE REACTIONS</td>
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<td>Hemolytic Anemia Associated with G6PD</td>
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<td>205552, 08/24/2022</td>
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<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion</td>
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<td>IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [see Clinical Studies (14.2)].</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma</td>
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<td>RESONATE</td>
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<td>(…) Thirty-two percent of patients had 17p deletion. (…)</td>
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<td>CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE</td>
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<td>RESONATE included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for del 17p CLL/SLL are shown in Table 22. (See Table 22)</td>
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<td>63-Month Follow-Up</td>
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<td>With an overall follow-up of 63 months, the median investigator-assessed PFS in patients with del 17p per IWCLL criteria was 40.6 months [95% CI (25.4, 44.6)]. In the IMBRUVICA arm versus 18.8 months [95% CI (14.6, 22.9)] in the ofatumumab arm, respectively. Overall response rate as assessed by investigators in patients with del 17p was 88.9% in the IMBRUVICA arm versus 18.8% in the ofatumumab arm.</td>
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<td>iLLUMINATE</td>
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<td>The iLLUMINATE study (a multi-center study of ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab) (NCT02294574) was conducted in patients with treatment naive CLL or SLL. Patients were 65 years of age or older or &lt; 65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance &lt; 70 mL/min, or presence of del 17p/TP53 mutation. (…)</td>
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<td>The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy included lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%). (…)</td>
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<td>In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].</td>
</tr>
</tbody>
</table>

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<td>205552, 08/24/2022</td>
<td>Ibrutinib (2)</td>
<td>Oncology</td>
<td>Chromosome 11q</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma</td>
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<td>RESONATE-2</td>
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<td>(…) The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic splenomegaly (37%), progressive or symptomatic hepatomegaly (30%), pancytopenia (27%), and night sweats (25%). (…)</td>
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<td>HELIOS</td>
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<td>(…) The median age was 64 years (range, 31 to 88 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor &gt; 5 cm and 26% presented with del11q. (…)</td>
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<td>FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 [see Clinical Pharmacology (12.3)].</td>
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<td>(…) At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status. (…)</td>
</tr>
<tr>
<td>205552, 08/24/2022</td>
<td>Ibrutinib (3)</td>
<td>Oncology</td>
<td>MYD88</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.3 Waldenström’s Macroglobulinemia</td>
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<td>INNOVATE</td>
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<td>(…) At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status. (…)</td>
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<tr>
<td>022192, 02/23/2017</td>
<td>Iloperidone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
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<td>Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6</td>
<td>FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 [see Clinical Pharmacology (12.3)].</td>
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<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.3 QT Prolongation</td>
<td>(…) Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism [see Drug Interactions (7.1)], and in patients with reduced activity of CYP2D6 [see Clinical Pharmacology (12.3)]. (…)</td>
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<td>7 DRUG INTERACTIONS</td>
<td>7.1 Potential for Other Drugs to Affect FANAPT</td>
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<td>Fluoxetine: Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2- to 3-fold, and decreased the AUC of its metabolite P96 by one-half. (…)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.3 Pharmacokinetics</td>
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<td>The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3-4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4. Metabolism and Elimination Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P86 and P88. The iloperidone metabolite P86 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. Approximately 7% - 10% of Caucasians and 3% - 5% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers. Coadministration of FANAPT with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3-fold increase in iloperidone plasma exposure, and therefore one-half of the FANAPT dose should be administered. Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs. The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 13.1% (EM) to 12.3% (PM).</td>
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</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>021588, 08/21/2018</td>
<td>Imatinib (1)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td><strong>1 INDICATIONS AND USAGE</strong></td>
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<td>1.6 Aggressive Systemic Mastocytosis (ASM)</td>
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<td>Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test [see Dosage and Administration (2.7)] or with c-Kit mutational status unknown.</td>
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<td>1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)</td>
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<td>Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.</td>
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<td>1.10 Adjuvant Treatment of GIST</td>
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<td>Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.</td>
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<td><strong>2 DOSAGE AND ADMINISTRATION</strong></td>
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<td>2.7 Adult Patients with ASM</td>
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<td>The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRA, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.</td>
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</table>

#### 14 CLINICAL STUDIES

**14.5 Myelodysplastic/Myeloproliferative Diseases**

An open-label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…)

**14.6 Aggressive Systemic Mastocytosis**

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…)

**14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia**

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…)

**14.8 Dermatofibrosarcoma Protuberans**

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…)

**14.9 Gastrointestinal Stromal Tumors**

One open-label, multinational Phase 2 study was conducted in patients with Kit (CD117) positive unresectable or metastatic malignant GIST, (…) Adjuvant Treatment of GIST

In the adjuvant setting, Gleevec was investigated in a multicenter, double-blind, placebo-controlled, randomized trial involving 713 patients (Study 1). Patients were randomized one to one to Gleevec at 400 mg/day for 12 months or matching placebo for 12 months. The ages of these patients ranged from 18 to 91 years. Patients were included who had a histologic diagnosis of primary GIST, expressing KIT protein by immunochemistry and a tumor size greater than or equal to 3 cm in maximum dimension with complete gross resection of primary GIST within 14 to 70 days prior to registration. (…)

**14.8** Aggressive Systemic Mastocytosis

Adjuvant treatment of adult patients with KIT (CD117) positive unresectable or metastatic malignant GIST, (…) A second randomized, multicenter, open-label, phase 3 trial in the adjuvant setting (Study 2) compared 12 months of Gleevec treatment to 36 months of Gleevec treatment at 400 mg/day in adult patients with Kit (CD117) positive GIST after surgical resection with one of the following: tumor diameter greater than 5 cm and mitotic count greater than 5/50 high power fields (HPF), or tumor diameter greater than 10 cm and any mitotic count, or tumor of any size with mitotic count greater than 10/50 HPF, or tumors ruptured into the peritoneal cavity. (…)

### Additional notes

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In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

2.3 Pediatric Patients with Ph+ CML CP

The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with Gleevec treatment in children under 1 year of age.

2.4 Adult Patients with Ph+ ALL

The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

2.5 Pediatric Patients with Ph+ ALL

The recommended dose of Gleevec to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m²/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose.

2.14 Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (…)

5 WARNINGS AND PRECAUTIONS

5.1 Fluid Retention and Edema

(…) In a randomized trial in patients with newly diagnosed Ph+CML in chronic phase comparing Gleevec and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Gleevec and in 3.9% of patients receiving nilotinib 300 mg bid. (…)

5.3 Congestive Heart Failure and Left Ventricular Dysfunction

(…) In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. In another randomized trial with newly diagnosed Ph+ CML patients in chronic phase that compared Gleevec and nilotinib, cardiac failure was observed in 1.1% of patient in the Gleevec arm and 2.2% of patients in the nilotinib 300 mg bid arm and severe (Grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. (…)

5.5 Hemorrhage

(…) Gastrointestinal tumor sites may have been the source of GI hemorrhages. In a randomized trial in patients with newly diagnosed Ph+CML in chronic phase comparing Gleevec and nilotinib, GI hemorrhage occurred in 1.4% of patients in the Gleevec arm, and in 2.9% of patients in the nilotinib 300 mg bid arm. None of these events were Grade 3 or 4 in the Gleevec arm; 0.7% were Grade 3 or 4 in the nilotinib 300 mg bid arm. In addition, gastric antral vascular ectasia has been reported in postmarketing experience.

6 ADVERSE REACTIONS

6.1 Chronic Myeloid Leukemia

The majority of Gleevec-treated patients experienced adverse reactions at some time. Gleevec was discontinued due to drug-related adverse reactions in 2.4% of patients receiving Gleevec in the randomized trial of newly diagnosed patients with Ph+CML in chronic phase comparing Gleevec versus IFN + Ara-C, and in 12.5% of patients receiving Gleevec in the randomized trial of newly diagnosed patients with Ph+ CML in chronic phase comparing Gleevec and nilotinib. (See Table 3) (…)

6.2 Adverse Reactions in Pediatric Population

In combination with multi-agent chemotherapy

(…) Patients with Ph+ ALL (n=92) were assigned to receive Gleevec and treated in 5 successive cohorts. Gleevec exposure was systematically increased in successive cohorts by earlier introduction and more prolonged duration.

The safety of Gleevec given in combination with intensive chemotherapy was evaluated by comparing the incidence of grade 3 and 4 adverse events, neutropenia (less than 750/mL) and thrombocytopenia (less than 75,000/mL) in the 92 patients with Ph+ ALL enrolled on the trial who did not receive Gleevec. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Gleevec. The protocol included up to 18 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Gleevec and 647 without Gleevec. The adverse events that were reported with a 5% or greater incidence in patients with Ph+ ALL compared to Ph- ALL or with a 1% or greater incidence in cycles of therapy administered with or without Gleevec are presented in Table 8. (See Table 8) (…)

6.4 Acute Lymphoblastic Leukemia

The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps and rash. Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb edemas. These edemas were reported as Grade 3/4 events in 6.3% of the patients and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec.

6.7 Hyperesinophilic Syndrome and Chronic Eosinophilic Leukemia

The safety profile the HES/CEL patient population does not appear to be different from the safety profile of Gleevec observed in other hematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC Grade 3 leucopenia, neutropenia, lymphopenia, and anemia.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

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<td>The safety and effectiveness of Gleevec have been demonstrated in pediatric patients with newly diagnosed Ph+ chronic phase CML and Ph+ ALL [see Clinical Studies (14.2, 14.4)]. There are no data in children under 1 year of age.</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Pediatric Use</td>
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<td>(…) Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, Ph+ ALL, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in pediatric patients receiving 260 mg/m² once-daily (not exceeding 400 mg once-daily) or 340 mg/m² once-daily (not exceeding 600 mg once-daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once-daily.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Chronic Myeloid Leukemia</td>
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<td>Chronic Phase, Newly Diagnosed</td>
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<td>An open-label, multicenter, international randomized Phase 3 study (Gleevec versus IFN+ara-C) has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (See Table 18) (…)</td>
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<td>(…) An open-label, multicenter, randomized trial (Gleevec versus nilotinib) was conducted to determine the efficacy of Gleevec versus nilotinib in adult patients with cytogenetically confirmed, newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. (See Table 19) (…)</td>
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<td>(…) Late Chronic Phase CML and Advanced Stage CML: Three international, open-label, single-arm phase 2 studies were conducted to determine the safety and efficacy of Gleevec in patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were black. In clinical studies, 38%-40% of patients were ≥60 years of age and 10%-12% of patients were ≥70 years of age. (…) Chronic Phase, Prior Interferon-Alpha Treatment: Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). (…)</td>
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<td>14.2 Pediatric CML</td>
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<td>One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. (…)</td>
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<td>(…) In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.</td>
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<td>14.3 Acute Lymphoblastic Leukemia</td>
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<td>A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease were studied, 43 of whom received the recommended Gleevec dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL received Gleevec 600 mg/day in a phase 1 study.</td>
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<td>Confirmed and unconfirmed hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 21. The median duration of hematologic response was 3.4 months and the median duration of MCRy was 2.3 months. (See Table 21) (…)</td>
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<td>14.4 Pediatric ALL</td>
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<td>Pediatric and young adult patients with very high risk ALL, defined as those with an expected 5-year event-free survival (EFS) less than 45%, were enrolled after induction therapy on a multicenter, non-randomized cooperative group pilot protocol.</td>
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<td>The safety and effectiveness of Gleevec (340 mg/m²/day) in combination with intensive chemotherapy was evaluated in a subgroup of patients with Ph+ ALL. The protocol included intensive chemotherapy and hematopoietic stem cell transplant after 2 courses of chemotherapy for patients with an appropriate HLA-matched family donor. There were 92 eligible patients with Ph+ ALL enrolled. (…)</td>
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<td>(…) There were 50 patients with Ph+ ALL assigned to cohort 5 all of whom received Gleevec plus chemotherapy; 30 were treated exclusively with chemotherapy and Gleevec and 20 received chemotherapy plus Gleevec and then underwent hematopoietic stem cell transplant, followed by further Gleevec treatment. (…)</td>
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<td>1 INDICATIONS AND USAGE</td>
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<td></td>
<td>1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)</td>
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<td>Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)].</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.6 Adult Patients with MDS/MPD</td>
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<td>Determine PDGFRb gene rearrangements status prior to initiating treatment. Information on FDA-approved tests for the detection of PDGFRb rearrangements is available at <a href="http://www.fda.gov/companiondiagnostics">http://www.fda.gov/companiondiagnostics</a>.</td>
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<td>The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.5 Myelodysplastic/Myeloproliferative Diseases</td>
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</tbody>
</table>

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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.

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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>021588, 08/21/2016</td>
<td>Imatinib (4)</td>
<td>Oncology</td>
<td>FIP1L1-PDGFRα</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
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<td>1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)</td>
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<td>Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.</td>
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<td>2.7 Adult Patients with ASM</td>
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<td>Determine D816V c-Kit mutation status prior to initiating treatment. Information on FDA-approved test for the detection of D816V c-Kit mutation is available at <a href="http://www.fda.gov/comparisons/diagnostics">http://www.fda.gov/comparisons/diagnostics</a>. The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If cKit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 300 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.</td>
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<td>2.8 Adult Patients with HES/CEL</td>
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<td>The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 300 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.</td>
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<td>2.14 Dose Adjustment for Hematologic Adverse Reactions</td>
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<td>Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1)(...)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.6 Aggressive Systemic Mastocytosis</td>
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<td>(...) Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality were predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phes522Cys and one K509I) and four patients had a D816V c-Kit mutation (not considered sensitive to Gleevec), one with concomitant CML. (See Table 23) (...)</td>
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<td>14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia</td>
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<td>One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (...)</td>
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<tr>
<td>017090, 07/28/2014</td>
<td>Imipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>Drug Interactions</td>
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<td>Drugs Metabolized by P450 2D6</td>
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<td>The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). (...)</td>
</tr>
</tbody>
</table>

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</table>
| 12/22/2021 | 214012                | Infigratinib        | Oncology          | FGR2       | Indication and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE

LEQVIO® is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

The effect of LEQVIO on cardiovascular morbidity and mortality has not been determined.

14 CLINICAL STUDIES

The efficacy of LEQVIO was investigated in three randomized, double-blind, placebo-controlled trials that enrolled 3457 adults with HeFH or clinical ASCVD, who were taking maximally tolerated statin therapy and who required additional LDL-C lowering. Demographics and baseline disease characteristics were balanced between the treatment arms in all trials. (…)

Heterozygous Familial Hypercholesterolemia (HeFH)

Study 3 (ORION-9, NC103397121) was a multicenter, double-blind, placebo-controlled 18-month trial in which 482 patients with HeFH were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 242) or placebo (n = 240) on Day 1, Day 90, Day 270, and at Day 450. Patients with HeFH were taking a maximally tolerated dose of statin with or without other lipid modifying therapy, and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria using either the Simon Broome or WHO/Dutch Lipid Network criteria. Patients were stratified by country and by current use of statins or other lipid-modifying therapies. Patients taking PCSK9 inhibitors were excluded from the trial. (See Table 4 and Figure 3)

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</tr>
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</table>
| 022383, 05/29/2019 | Indacaterol           | Pulmonary           | UGT1A1            |            | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.4 Pharmacogenomics

The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as *28) and the (TA)6, (TA)7 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.

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</table>
| 761142, 06/11/2020 | Inebilizumab-eton     | Neurology           | AQP4              |            | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE

UPLIZNA is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

14 CLINICAL STUDIES

The efficacy of UPLIZNA for the treatment of NMOSD was established in Study 1 (NCT02200770), a randomized (3:1), double-blind, placebo-controlled trial that enrolled 213 patients with NMOSD who were anti-AQP4 antibody positive and 17 who were anti-AQP4 antibody negative. (…)

Of the 213 enrolled anti-AQP4 antibody positive patients, a total of 161 were randomized to receive treatment with UPLIZNA, and 52 were randomized to receive placebo. (…) The time to the first adjudicated relapse was significantly longer in patients treated with UPLIZNA compared to patients who received placebo (relative risk reduction 73%; hazard ratio: 0.272; p < 0.0001). In the anti-AQP4 antibody positive population there was a 77.3% relative reduction (hazard ratio: 0.227, p < 0.0001). There was no evidence of a benefit in patients who were anti-AQP4 antibody negative. (See Table 4 and Figure 1)

Compared to placebo-treated patients, patients treated with UPLIZNA who were anti-AQP4 antibody positive had reduced annualized rates of hospitalizations (0.11 for UPLIZNA versus 0.50 for placebo).

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| 05/28/2021, 214622 | Infigratinib         | Oncology            | FGR2              |            | Indication and Usage, Clinical Studies | 1 INDICATIONS AND USAGE

TRUSELTIQ is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

14 CLINICAL STUDIES

14.1 Cholangiocarcinoma

Study CBGJ388X2204 (NCT02150967), a multicenter open-label single-arm trial, evaluated the efficacy of TRUSELTIQ in 108 patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as determined for enrollment by local [89%] or central testing [11%]. Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17 exon 18 of the FGFR2 gene that leaves the FGFR2 kinase domain intact. (…)

The median age was 53 years (range: 23 to 81 years), 62% were female, 72% were White, 3.7% were Black or African American, 10% were Asian, and 99% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42%) or 1 (57%). The presence of FGFR2 fusions or other rearrangements was determined in 104 enrolled patients (96%) with Next Generation Sequencing (NGS) testing. Eighty-eight (81%) patients had in-frame FGFR2 fusions, and BIC1 the most commonly reported fusion partner (n=27, 25%). Twenty (19%) patients had other FGFR2 rearrangements that may not be in-frame with the partner gene or the partner gene was not identifiable.

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<tr>
<td>211172, 10/05/2018</td>
<td>Inotersen</td>
<td>Neurology</td>
<td>TTR</td>
<td>Adverse Reactions, Clinical Pharmacology</td>
<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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</tbody>
</table>
|                                        | | | | | (…) Baseline disease characteristics were largely similar in TEGSedi-treated patients and patients in the placebo control group. Sixty-seven percent of patients were in Stage 1 of the disease at baseline, and 33% in Stage 2. Fifty-two percent of patients had Val30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different other point mutations. (…)
|                                        | | | | | 12 CLINICAL PHARMACOLOGY |
|                                        | | | | | 12.2 Pharmacodynamics |
|                                        | | | | | The pharmacodynamic effects of TEGSedi were evaluated in hATTR amyloidosis patients treated with 284 mg TEGSedi via subcutaneous injection once weekly. With repeat dosing, the mean percent decreases from baseline in serum TTR from Week 13 to Week 65 of treatment ranged from 68% to 74% (median range: 75% to 79%). Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race. (…)
| 761040, 08/17/2017                     | Ozogamicin | Oncology | BCR-ABL1 (Philadelphia chromosome) | Clinical Studies | 14 CLINICAL STUDIES |
|                                        | | | | | 14.1 Unsectactable or Metastatic Melanoma |
|                                        | | | | | The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094653) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund’s adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A*02:01:01 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. (…)
| 125377, 11/13/2020                     | Ipilimumab (1) | Oncology | HLA-A | Clinical Studies | 14 CLINICAL STUDIES |
|                                        | | | | | 14.1 Unsectactable or Metastatic Melanoma |
|                                        | | | | | The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094653) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund’s adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A*02:01:01 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. (…)
| 125377, 11/13/2020                     | Ipilimumab (2) | Oncology | Microsatellite Instability, Mismatch Repair | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE |
|                                        | | | | | 1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer |
|                                        | | | | | YERVOY; in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.4)]. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. |
|                                        | | | | | 2 DOSAGE AND ADMINISTRATION |
|                                        | | | | | 2.2 Recommended Dosage |
|                                        | | | | | The recommended dosages of YERVOY as a single agent are presented in Table 1. (See Table 2) |
|                                        | | | | | 5 WARNINGS AND PRECAUTIONS |
|                                        | | | | | 5.5 Risks Associated When Administered in Combination with Nivolumab |
|                                        | | | | | YERVOY is indicated for use in combination with nivolumab for patients with advanced RCC, MSI-H or dMMR mCRC, HCC, and NSCLC. Refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment. |
|                                        | | | | | 6 ADVERSE REACTIONS |
|                                        | | | | | 6.1 Clinical Trials Experience |
|                                        | | | | | The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIIC (with or in-transit metastases) cutaneous melanoma; and to YERVOY 1 mg/kg, administered in combination with nivolumab, in two trials: CHECKMATE-214 (NCT02231748), a randomized trial in previously untreated patients with advanced renal cell carcinoma, and CHECKMATE-142 (NCT02060188), an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer. (…)
|                                        | | | | | Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer |
|                                        | | | | | The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, nonrandomized, multiple parallel-cohort study. In CHECKMATE-142, 119 patients with previously treated MSI-H or dMMR mCRC received YERVOY, in combination with nivolumab, in a single-arm cohort. In another single-arm cohort under CHECKMATE-142, 74 patients with mCRC received nivolumab monotherapy. (See Tables 9 and 10) (…)
|                                        | | | | | 8 USE IN SPECIFIC POPULATIONS |
|                                        | | | | | 8.4 Pediatric Use |

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<td>125377, 11/13/2020</td>
<td>Ipilimumab (3)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>NDS indicator and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies</td>
</tr>
</tbody>
</table>

The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma or for the treatment of microsatellite instability-high ( MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY in this age group is supported by evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacoepidemiologic data demonstrating that the exposure at doses of 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of advanced melanoma and MSI-H or dMMR metastatic colorectal cancer are sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients. (…) 

14 CLINICAL STUDIES
14.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallelcohort, open-label study conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG PS 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Participants enrolled in the YERVOY and nivolumab MSI-H mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks. Participants enrolled in the single-agent nivolumab MSI-H mCRC cohort received nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (See Table 22) (…) 

14.3 Previously Untreated Advanced Renal Cell Carcinoma
CHECKMATE-214 (NCT02321749) was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. (…) (…) Efficacy results from CHECKMATE-214 are presented in Table 21 and Figure 3. In intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to YERVOY and nivolumab arm compared with sunitinib arm. OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. (…) 

14.6 Metastatic Non-Small Cell Lung Cancer
First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Exposing PD-L1 (≥1%); In Combination with Nivolumab
CHECKMATE-227 (NCT02471926) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer (ASLC) classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. (…) Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). (…) In Part 1a, a total of 793 patients were randomized to receive either YERVOY in combination with nivolumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients 65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline

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<td>ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers. The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the YERVOY and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 22 and Figure 4. (See Table 24 and Figure 4) First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. (…) Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m2, or cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus &lt;1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. (…) A total of 719 patients were randomized to receive either YERVOY in combination with nivolumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was &lt;1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 80% were former or current smokers. (…) 14.7 Malignant Pleural Mesothelioma (…) A total of 605 patients were randomized to receive either YERVOY in combination with nivolumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89), with 72% of patients ≥65 years and 26% ≥75 years, 85% were White, 11% were Asian, and 77% were male. Baseline ECOG performance status was 0 (40%) or 1 (60%), 35% had Stage III and 51% had Stage IV disease, 75% had epithelioid and 25% had non-epithelioid histology, 75% had tumors with PD-L1 expression ≥1%, and 22% had tumors with PD-L1 expression &lt;1%.</td>
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<td>1 INDICATIONS AND USAGE 1.6 Metastatic Non-Small Cell Lung Cancer YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations. YERVOY, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations. 6 ADVERSE REACTIONS The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (&gt;1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma; to YERVOY 1 mg/kg, administered in combination with nivolumab, in three trials: CHECKMATE227, a randomized trial in previously untreated patients with advanced renal cell carcinoma, CHECKMATE-142, an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer, and CHECKMATE-227, a randomized, multicenter, multicohort, open-label trial in patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations; and to YERVOY 3 mg/kg, administered in combination with nivolumab, in CHECKMATE-040, a multicenter, multiple cohort, open-label trial conducted in patients with hepatocellular carcinoma who progressed on or were intolerant to sorafenib; and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, an open-label, multicenter, randomized trial in adult patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations. (…) First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.6)]. (…) 14 CLINICAL STUDIES 14.6 Metastatic Non-Small Cell Lung Cancer First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. (…) First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublt Chemotherapy CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. (…)</td>
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1 INDICATIONS AND USAGE

1.6 Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations. YERVOY, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

6 ADVERSE REACTIONS

The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIE (with no in-transit metastases) cutaneous melanoma; to YERVOY 1 mg/kg, administered in combination with nivolumab, in three trials: CHECKMATE227, a randomized trial in previously untreated patients with advanced renal cell carcinoma, CHECKMATE-142, an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer, and CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations; and to YERVOY 3 mg/kg, administered in combination with nivolumab, in CHECKMATE-040, a multicenter, multiple cohort, open-label trial conducted in patients with hepatocellular carcinoma who progressed on or were intolerant to sorafenib; and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, an open-label, multicenter, randomized trial in adult patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations. (…)

First-line Treatment of Metastatic NSCLC in Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations (see Clinical Studies (14.6)). (…)

14 CLINICAL STUDIES

14.6 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [IASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. (…)

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doubled Chemotherapy

CHECKMATE-9LA (NCT02521570) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. (…)

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</table>
| 020571, 01/27/2022                     | irinotecan | Oncology | UGT1A1 | Dosage and Administration, Warnings and Precautions, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.3 Dosage in Patients with Reduced UGT1A1 Activity
When administered in combination with other agents, or as a single-agent, consider a reduction in the starting dose by at least one level of CAMPTOSAR for patients known to be homozygous for the UGT1A1*28 or *6 alleles (*28/*28, *6/*6) or compound heterozygous for the UGT1A1*28 and *6 alleles (*6/*28) [see Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3, 12.5)]. Subsequent dosage modifications may be required based on individual patient tolerance to treatment [see Dosage and Administration (2.1, 2.2)]. |

5 WARNINGS AND PRECAUTIONS
5.3 Increased Risk of Neutropenia in Patients With Reduced UGT1A1 Activity
Published studies have shown that individuals who are homozygous for either the UGT1A1*28 or *6 alleles (*28/*28, *6/*6) or who are compound or double heterozygous for the UGT1A1*28 and *6 alleles (*9/*28) are at increased risk for severe or life-threatening neutropenia during treatment with CAMPTOSAR. These individuals are UGT1A1 poor metabolizers and experience increased systemic exposure to SN-38, an active metabolite of irinotecan. Individuals who are heterozygous for either the UGT1A1*28 or *6 alleles (*1/*28, *1/*6) are intermediate metabolizers and may also have an increased risk of severe or life-threatening neutropenia [see Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.3), and Clinical Pharmacology (12.5)]. Consider UGT1A1 genotype testing for the *28 and *6 alleles to determine UGT1A1 metabolizer status [see Clinical Pharmacology (12.5)]. When administering CAMPTOSAR, consider a reduction in the CAMPTOSAR starting dose by at least one level for patients known to be homozygous or compound heterozygous for the UGT1A1*28 and/or *6 alleles (*28/*28, *6/*6, *6/*28). Closely monitor patients with UGT1A1*28 or *6 alleles for neutropenia during and after treatment with CAMPTOSAR. The precise dosage reduction in this patient population is not known. Subsequent dosage modifications may be required based on individual patient tolerance to treatment [see Dosage and Administration (2.1, 2.2)]. |

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism
Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases that form an active metabolite SN-38, and UGT1A1 which mediates the glucuronidation of SN-38 to form an inactive metabolite. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38. Patients who are homozygous for either the UGT1A1*28 or *6 alleles, or who are compound heterozygous for these alleles, have higher SN-38 AUC than patients with the wild-type UGT1A1 alleles [see Dosage and Administration (2.3), Warnings and Precautions (5.3), and Clinical Pharmacology (12.5)]. Irinotecan can also undergo CYP3A-mediated oxidative metabolism to several inactive metabolites, one of which can be hydrolyzed by carboxylesterase to release the active metabolite SN-38. |

12.5 Pharmacogenomics
The active metabolite SN-38 is further metabolized via UGT1A1. Genetic variants of the UGT1A1 gene such as the UGT1A1*28 [(TA)7] and *6 alleles lead to reduced UGT1A1 enzyme expression or activity and decreased function to a similar extent. Individuals who are homozygous or compound (double) heterozygous for these alleles (e.g., *28/*28, *6/*6, *28/*28) are UGT1A1 poor metabolizers and are at increased risk for severe or life-threatening neutropenia from CAMPTOSAR due to elevated systemic exposure to SN-38. The UGT1A1*6/*6 genotype should not be confused with 6/6 genotype, which is sometimes used to represent the genotype of individuals who are wild-type for UGT1A1*28. Individuals who are heterozygous for either the UGT1A1*28 or *6 alleles (*1/*28, *1/*6, *1/*28) are UGT1A1 intermediate metabolizers and may also have an increased risk of severe or life-threatening neutropenia [see Dosage and Administration (2.3), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]. Published studies have shown that individuals with UGT1A1*28 and *6 alleles may be at an increased risk of severe diarrhea. The risk evidence appears greater in UGT1A1*28 and *6 homozygous patients and in those taking irinotecan doses > 125 mg/m2 [see Warnings and Precautions (5.1)]. UGT1A1*28 and *6 alleles occur at various frequencies in different populations. Approximately 20% of Black or African American, 10% of White, and 2% of East Asian individuals are UGT1A1*28 or *6 alleles [see Clinical Pharmacology (12.5)]. |

761113, 03/02/2020
| Isatuximab-irfc | Oncology | Chromosome 17p | Clinical Studies | 14 CLINICAL STUDIES
14.1 Multiple Myeloma
CARUS-MM
[…]
Overall, 20% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12%, 8% and 2% of patients, respectively. (…)
 |
761113, 03/02/2020
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<td>Isosflurane</td>
<td>Anesthesiology</td>
<td>CACNA1S, RYR1 (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>CONTRAINDICATIONS Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.</td>
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| 050705, 02/28/2019                     | Isoniazid, Pyrazinamide, and Rifampin | Infectious Diseases | Nonspecific (NAT) | Clinical Pharmacology | CLINICAL PHARMACOLOGY  (

  (...) Isoniazid is metabolized in the liver mainly by acetylation and dehydroxidation. The rate of acetylation is genetically determined. Approximately 50% of African Americans and Caucasians are “slow inactivators” and the rest are “rapid inactivators”; the majority of Eskimos and Asians are “rapid inactivators.” The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions. |
| 019790, 10/24/2014                     | Isosorbide Dinitrate          | Cardiology        | CYB5R      | Overdosage        | OVERDOSE |

  Methemoglobinemia

  Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide dinitrate are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide dinitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8-6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously. |
| 020215, 10/02/2014                     | Isosorbide Mononitrate        | Cardiology        | CYB5R      | Overdosage        | OVERDOSE |

  Methemoglobinemia

  Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide mononitrate are quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2.4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8-11.1 mg of bioavailable isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously. |
| 203188, 04/29/2019                     | Ivcator                       | Pulmonary         | CFTR       | 1 INDICATIONS AND USAGE |

  KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (143)]. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation that may be associated with MHS. Variant pathogenicity should be assessed based on prior clinical experience, functional studies, prevalence information, or other evidence (see CONTRAINDICATIONS, WARNINGS). |
|                                           |                               |                   |            | 6 ADVERSE REACTIONS |

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of KALYDECO is based on pooled data from three placebo-controlled clinical trials conducted in 353 patients 6 years of age and older with CF who had a G551D mutation in the CFTR gene (Trials 1 and 2) or were homozygous for the F508del mutation (Trial 3). In addition, the following clinical trials have also been conducted (see Clinical Pharmacology (12) and Clinical Studies (14)):

- A 24-week, placebo-controlled trial (Trial 5) involving 69 patients between the ages of 6 and 68 years with an R117H mutation in the CFTR gene.
- A 24-week, open-label trial (Trial 6) in 34 patients 2 to less than 6 years of age. Patients eligible for Trial 6 were those with the G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. Of 34 patients enrolled, 32 had the G551D mutation and 2 had the S549N mutation.
- An 8-week, crossover design trial (Trial 7) involving patients between the ages of 12 and 72 years who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO.
- A cohort of 19 patients aged 12 months to less than 24 months, and a cohort of 11 patients aged 6 months to less than 12 months in a 24-week, open-label clinical trial in patients with CF aged less than 24 months (Trial 8).
- Of the 353 patients included in the pooled analyses of patients with CF who had either a G551D mutation or were homozygous for the F508del mutation in the CFTR gene, 50% of patients were female and 97% were Caucasian; 221 received KALYDECO, and 132 received placebo from 16 to 48 weeks. (…)

The incidence of adverse reactions below is based upon two double-blind, placebo-controlled, 48-week clinical trials (Trials 1 and 2) in a total of 213 patients with CF ages 6 to 53 who have a G551D mutation in the CFTR gene and who were treated with KALYDECO 150 mg orally or placebo twice daily. Table 2 shows adverse reactions occurring in ≥28% of KALYDECO-treated patients with CF who have a G551D mutation in the CFTR gene that also occurred at a higher rate than in the placebo-treated patients in the two double-blind, placebo-controlled trials. (See Table 2) (…)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

KALYDECO is indicated for the treatment of CF in pediatric patients 6 months to 17 years of age who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data (see Clinical Pharmacology (12.1) and Clinical Studies (14)).

Placebo-controlled clinical trials established efficacy and safety in the following pediatric patients with CF:


12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CFTR Chloride Transport Assay in Fisher Rat Thyroid (FRT) cells expressing mutant CFTR

In order to evaluate the response of mutant CFTR protein to ivacaftor, total chloride transport was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual CFTR mutations. Ivacaftor increased chloride transport in FRT cells expressing CFTR mutations that result in CFTR protein being delivered to the cell surface.

Data shown in Figure 1 are the mean (n=3-7) net change over baseline in CFTR-mediated chloride transport following the addition of ivacaftor in FRT cells expressing mutant CFTR proteins. The in vitro CFTR chloride response threshold was designated as a net increase of at least 10% of normal over baseline (dotted line) because it is predictive or reasonably expected to predict clinical benefit. Mutations with an increase in chloride transport of 10% or greater are considered responsive. A patient must have at least one CFTR mutation responsive to ivacaftor to be indicated.

Mutations including F508del that are not responsive to ivacaftor potentiation, based on the in vitro CFTR chloride response threshold, are listed in Figure 1 below the dotted line. (see Figure 1) Note that splice mutations cannot be studied in this FRT assay and are not included in Figure 1. Evidence of clinical efficacy exists for non-canonical splice mutations 2789+5G→A, 3272→G, 3849+10kbC→T, 711+3A→G and E831X and these are listed in Table 3 below (see also Clinical Studies (14.4)). The G970R mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor (see Clinical Studies (14.2)).

Ivacaftor also increased chloride transport in cultured human bronchial epithelial (HBE) cells derived from CF patients who carried F508del on one CFTR allele and either G551D or R117H on the second CFTR allele. (…)

Table 3 lists mutations that are responsive to ivacaftor based on 1) a positive clinical response and/or 2) iv in vitro data in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal). (see Table 3)

12.2 Pharmacodynamics

Sweat Chloride Evaluation

Changes in sweat chloride (a biomarker) response to KALYDECO were evaluated in seven clinical trials (see Clinical Studies (14)). In a two-part, randomized, double-blind, placebo-controlled, crossover clinical trial in patients with CF who had a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene (Trial 4), the treatment difference in mean change in sweat chloride from baseline through 8 weeks of treatment was -49 mmol/L (95% CI -57, -41). The mean changes in sweat chloride for the mutations for which KALYDECO is indicated ranged from -51 to -41, whereas the range for individual subjects with the G970R mutation was -1 to -11 mmol/L. In an open-label clinical trial in 34 patients ages 2 to less than 6 years administered either 50 mg or 75 mg of ivacaftor twice daily (Trial 6), the mean absolute change from baseline in sweat chloride through 24 weeks of treatment was -45 mmol/L, (95% CI

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<th>206038, 08/15/2018</th>
<th>Ivacaftor and Lumacaftor</th>
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<th>CFTR</th>
<th>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</th>
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<td><strong>1 INDICATIONS AND USAGE</strong></td>
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<td>ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. Limitations of Use</td>
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<td>The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation.</td>
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<td><strong>6 ADVERSE REACTIONS</strong></td>
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<td><strong>6.1 Clinical Trials Experience</strong></td>
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<td>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The overall safety profile of ORKAMBI is based on the pooled data from 1108 patients with CF 12 years and older who are homozygous for the F508del mutation in the CFTR gene who received at least one dose of study drug in 2 double-blind, placebo-controlled, Phase 3 clinical trials, each with 24 weeks of treatment (Trials 1 and 2). In addition, the following clinical trials have been conducted:</td>
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<tr>
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<td>A 24-week open-label trial (Trial 3) in 58 patients with CF aged 6 through 11 years homozygous for the F508del-CFTR mutation.</td>
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<tr>
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<td>A 24-week, placebo-controlled trial (Trial 4) in 204 patients aged 6 through 11 years homozygous for the F508del-CFTR mutation.</td>
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<td>A 24-week, open label trial (Trial 5) in 46 patients aged 12 years and older homozygous for the F508del-CFTR mutation and with advanced lung disease</td>
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<td><strong>210491, 02/12/2018</strong></td>
<td>Ivacaftor and Tezacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.</td>
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</table>

**8.4 Pediatric Use**

- The efficacy of ORKAMBI in children ages 2 through 11 years is extrapolated from efficacy in patients ages 12 years and older who are homozygous for the F508del mutation in the CFTR gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 2 through 11 years [see Clinical Pharmacology (12.3)].

**14 CLINICAL STUDIES**

**Confirmatory**

- The efficacy of ORKAMBI in patients with CF who are homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, 12-week clinical trials (Trials 1 and 2) in 1108 clinically stable patients with CF of whom 369 patients received ORKAMBI twice daily. (…)

**6 ADVERSE REACTIONS**

- (…) The safety profile for the CF patients enrolled in Trial 2 who were homozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor was similar to that observed in Trials 1 and 3.

**8 USE IN SPECIFIC POPULATIONS**

**8.4 Pediatric Use**

- SYMDEKO is indicated for the treatment of CF in pediatric patients ages 12-17 years who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. Clinical trials included the following CF patients: • 12 to 17 years of age who are homozygous for the F508del mutation (see Adverse Reactions (6) and Clinical Studies (14)); • 12 to 17 years of age who are heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)]. The safety and efficacy of SYMDEKO in patients with CF younger than 12 years of age have not been studied.

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacokinetics**

- Effects on Sweat Chloride

  In Trial 1 (patients homozygous for the F508del mutation), the treatment difference between SYMDEKO and placebo in mean absolute change from baseline in sweat chloride through Week 24 was -10.1 mmol/L (95% CI: -11.4, -8.8). In Trial 2 (patients heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor), the treatment difference in mean absolute change from baseline in sweat chloride through Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) between SYMDEKO and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo. (…)

**14 CLINICAL STUDIES**

**Dose Ranging**

- Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF (homozygous for the F508del mutation) 18 years of age and older with a screening ppFEV1<0.4. In the study, 34 and 100 patients, respectively, received tezacaftor at the daily doses of 10 mg, 30 mg, 100 mg, or 150 mg alone or in combination with ivacaftor 150 mg q12h, and 33 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean ppFEV1 change from baseline were observed with tezacaftor in combination with ivacaftor. Tezacaftor/ivacaftor in general had a greater mean treatment effect than tezacaftor alone. No additional benefit was observed at tezacaftor doses greater than 100 mg daily.

**Efficacy**

- The efficacy of SYMDEKO in patients with CF aged 12 years and older was evaluated in three Phase 3, double-blind, placebo-controlled trials (Trials 1, 2, and 3). Trial 1 was a 24-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were homozygous for the F508del mutation in the CFTR gene. Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in CF patients who were heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Mutations predicted to be responsive were selected for the study based on the clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro responsiveness to tezacaftor/ivacaftor [see Clinical Studies (14.2)]. Patients were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo. Trial 3 was a 12-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro testing to tezacaftor and/or ivacaftor. (…)

**14.1 Trial in Patients with CF Who Were Homozygous for the F508del Mutation in the CFTR Gene (Trial 1)**

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| 211192, 10/24/2023                     | idenib | Oncology | IDH1 | Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies | Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 28.3 years). The mean ppFEV1 at baseline was 60.0% (range: 27.8% to 96.2%). (see Table 8 and Figure 2) (…)

### 12.2 Pharmacodynamics

- Multiple doses of ivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies to levels similar to those observed at baseline in healthy subjects. In bone marrow, 2-HG concentrations were reduced by ≥90%.
- Cardiac Electrophysiology
  - A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state Cmax following a 500 mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 156 patients with relapsed or refractory AML, who received TIBSOVO 500 mg daily (see Warnings and Precautions (5.1)). Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline.

### 14 CLINICAL STUDIES

- TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory myelodysplastic syndromes (MDS) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)].
- TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults ≥75 years and older, or who have comorbidities that preclude use of intensive induction chemotherapy [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)].

### 14.3 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/Ivacaftor

In an analysis of BMI at Week 8, an exploratory endpoint, patients treated with SYMDEKO had a mean improvement of 0.2 kg/m² [95% CI (0.0, 0.3)], 0.1 kg/m² [95% CI (-0.1, 0.3)], and 0.3 kg/m² [95% CI (0.1, 0.5)] versus placebo for the overall, splice, and nonsense mutation populations of patients, respectively.

### 14.3 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/Ivacaftor

Tibsovo is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)].

### 14.4 Locally Advanced or Metastatic Cholangiocarcinoma

Tibsovo is indicated for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.3)].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Select patients for treatment with Tibsovo based on the presence of IDH1 mutations [see Clinical Studies (14.1, 14.2, 14.3, 14.4)]. Information on FDA-approved tests for the detection of IDH1 mutations in AML, MDS, and cholangiocarcinoma is available at http://www.fda.gov/CompanionDiagnostics.

#### 12.2 Pharmacodynamics

- Multiple doses of ivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies to levels similar to those observed at baseline in healthy subjects. In bone marrow, 2-HG concentrations were reduced by ≥90%.
- Cardiac Electrophysiology
  - A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state Cmax following a 500 mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 156 patients with relapsed or refractory AML, who received Tibsovo 500 mg daily (see Warnings and Precautions (5.1)). Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline.

#### 14 CLINICAL STUDIES

- Tibsovo is indicated for the treatment of adult patients with relapsed or refractory myelodysplastic syndromes (MDS) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.3)].

#### 14.1 Newly-Diagnosed AML

Newly diagnosed AML in combination with azacitidine

The efficacy of Tibsovo was evaluated in a randomized (1:1), multicenter, double-blind, placebo-controlled clinical trial (Study AG120-C-009, NCT03173248) of 146 adult patients with newly-diagnosed AML with an IDH1 mutation who were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2; severe

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| 022065, 10/18/2011                      | Ixabepilone (1) | Oncology         | ERBB2 (HER2) | Clinical Studies | 14 CLINICAL STUDIES Combination Therapy (...)
Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6. (...)

Monotherapy HER2-positive patients must also have progressed during or after discontinuation of trastuzumab. In this study, the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 45% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%.

| 022065, 10/18/2011                      | Ixabepilone (2) | Oncology         | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES Combination Therapy (...)
Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6. (...)

Monotherapy HER2-positive patients must also have progressed during or after discontinuation of trastuzumab. In this study, the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 45% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%.

| 204839, 04/28/2016                       | Lacosamide      | Neurology        | CYP2C19       | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Special Populations CYP2C19 Polymorphism |

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| 020406, 06/07/2018                     | Lansoprazole | Gastroenterology | CYP2C19 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS 7.3 Tacrolimus Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Drug-Drug Interactions Tacrolimus Tacrolimus is metabolized by the cytochrome P450 (CYP) 3A4 enzyme, which is primarily involved in the metabolism of tacrolimus. The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John’s wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) or from 1,500 mg/day up to 1,000 mg/day (hormone receptor-positive breast cancer indication). Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability. (…)

| 020259, 12/06/2018                     | Lapatinib (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE TYKERB® is indicated in combination with: • capcitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capcitabine. • letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer. 2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosing HER2-Positive Metastatic Breast Cancer The recommended dose of TYKERB is 1,250 mg given orally once daily on Days 1-21 continuously in combination with capcitabine 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended (see Clinical Pharmacology (12.3)). Capcitabine should be taken with food or within 30 minutes after food. If a day’s dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs. Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended (see Clinical Pharmacology (12.3)). 2.2 Dose Modification Guidelines Hepatic Impairment Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability. (…)

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience HER2-Positive Metastatic Breast Cancer The safety of TYKERB has been evaluated in more than 12,000 patients in clinical trials. (…)

|                  |                  |                  |                  |                  |                  |

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<td>022059, 12/06/2018</td>
<td>Lapatinib (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
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</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use
Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (…) 

14 CLINICAL STUDIES
14.1 HER2-Positive Metastatic Breast Cancer
The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab. (…) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor positive (ER+) or progesterone receptor positive (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab. (…) Clinical Studies Describing Limitation of Use: In two randomized trials, TYKERB based chemotherapy regimens have been shown to be less effective than trastuzumab-based chemotherapy regimens. The first randomized, open-label study compared the safety and efficacy of TYKERB in combination with capecitabine relative to trastuzumab in combination with capecitabine in women with HER2-positive metastatic breast cancer (N = 546). (…)

(…) The second randomized, open-label study compared the safety and efficacy of taxane-based chemotherapy plus TYKERB to taxane-based chemotherapy plus trastuzumab as first-line therapy in women with HER2-positive, metastatic breast cancer (N = 652). (…)

14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer
The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PGR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). Of all patients randomized to treatment, 219 (17%) patients had tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH) ≥2 or ≥3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2 negative and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective was to evaluate and compare progression-free survival (PFS) in the HER2-positive population. Progression-free survival was defined as the interval of time between date of randomization and the earlier date of first documented sign of disease progression or death due to any cause. The baseline demographic and disease characteristics were balanced between the two treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty-four percent (84%) of the patients were white. Approximately 50% of the HER2-positive population had prior adjuvant/neoadjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab. In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (See Table 8 and Figure 3) The efficacy and safety of TYKERB, in combination with an aromatase inhibitor (AI), were confirmed in another randomized Phase 3 trial. Patients enrolled were post-menopausal women who had hormone receptor positive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior trastuzumab containing chemotherapy and endocrine therapies. (…) The study was designed to evaluate a potential benefit in Progression Free Survival (PFS) when double versus single HER2 targeted therapy was administered in combination with an AI (letrozole, exemestane, or anastrozole). The major efficacy outcome measure was PFS based on local radiology/investigator’s assessment comparing TYKERB + trastuzumab + AI versus trastuzumab + AI. (…)

1 INDICATIONS AND USAGE
TYKERB is indicated in combination with: (…) letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. (…) 

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer
The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)].

2.2 Dose Modification Guidelines
Hepatic Impairment
Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range and should be considered. However, there are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Concomitant Strong CYP3A4 inducers

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<td>12.5 Pharmacogenomics</td>
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<td>The HLA alleles DQA1<em>02:01 and DRB1</em>07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT &gt;5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DQA1<em>02:01 or DRB1</em>07:01 allele carriers was 8% versus 0.5% in non-carriers. These HLA alleles are present in approximately 15% to 25% of Caucasian, Asian, African, and Hispanic populations and 1% in Japanese populations. Liver function should be monitored in all patients receiving therapy with TYKERB regardless of genotype.</td>
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<td>210861,</td>
<td>Larotrectinib</td>
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<td>NTRK</td>
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<td>1 INDICATIONS AND USAGE</td>
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<td>11/23/2022</td>
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<td>VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:</td>
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<td>• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion with a known acquired resistance mutation, (…)</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection Select patients for treatment with VITRAKVI based on the presence of a NTRK gene fusion in tumor specimens [see Clinical Studies (14)]. Information on FDA-approved tests is available at <a href="http://www.fda.gov/companiondiagnostics">http://www.fda.gov/companiondiagnostics</a>.</td>
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<td>Lecanemab-irmb</td>
<td>Neurology</td>
<td>APOE</td>
<td>Boxed Warning, Warnings and Precautions, Clinical Studies, Patient Counseling Information</td>
<td>BOXED WARNING APOE ε4 Homozygotes Patients who are apolipoprotein E ε4 (APOE ε4) homozygotes (approximately 15% of Alzheimer’s disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA [see Warnings and Precautions (5.1)]. Consider the benefit of LEQEMBI for the treatment of Alzheimer’s disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI [see Warnings and Precautions (5.1) and Clinical Studies (14)].</td>
</tr>
</tbody>
</table>

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Among these 279 patients, the median age was 46 years (range: 0.1 days to 84 years); 33% were younger than 18 years; 48% were male; and 74% were White. 9% were Hispanic/Latino, 7% were Asian and 6% were Black. The most common tumors (33%) in order of decreasing frequency were soft tissue sarcoma (17%), thyroid (13%), infantile fibrosarcoma (12%), primary central nervous system (CNS) (11%), salivary gland (9%), lung (9%), colon (6%), breast (4%), or melanoma (3%). NTRK gene fusions were confirmed or inferred in 75% of VITRAKVI-treated patients. (…)

14 CLINICAL STUDIES
The efficacy of VITRAKVI was evaluated in pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials: Study LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). (…)

The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). A total of 50 patients had NTRK gene fusions detected by NGS and 5 patients had NTRK gene fusions detected by FISH. Efficacy results are summarized in Tables 4, 5, and 6.

5 WARNINGS AND PRECAUTIONS
5.1 Amyloid-Related Imaging Abnormalities
Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer’s disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with LEQEMBI. Consider the benefit of LEQEMBI for the treatment of Alzheimer’s disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI [see Warnings and Precautions (5.1) and Clinical Studies (14)].

Consider the benefit of LEQEMBI for the treatment of Alzheimer’s disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI. Incidence of ARIA Symptomatic ARIA occurred in 3% (29/898) of patients treated with LEQEMBI in Study 2 [see Clinical Studies (14)]. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI. Clinical symptoms associated with ARIA resolved in 7% (23/29) of patients during the period of observation. Similar findings were observed in Study 1. Including asymptomatic radiographic events, ARIA was observed in 21% (191/898) of patients treated with LEQEMBI, compared to 9% (84/979) of patients on placebo in Study 2. ARIA-E was observed in 13% (113/898) of patients treated with LEQEMBI compared to 2% (15/897) of patients on placebo. ARIA-H was observed in 17% (152/898) of patients treated with LEQEMBI compared with 9% (80/897) of patients on placebo. There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo. ApoE ε4 Carrier Status and Risk of ARIA Approximately 15% of Alzheimer’s disease patients are ApoE ε4 homozygotes. In Study 2, 16% (141/888) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (478/898) were heterozygotes, and 31% (278/898) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (45% on LEQEMBI vs. 22% on placebo) than in heterozygotes (19% on LEQEMBI vs 9% on placebo) and noncarriers (13% on LEQEMBI vs 4% on placebo). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers [see Dosage and Administration (2.3)]. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the

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This table includes information regarding Pharmacomogentic Biomarkers in Drug Labeling. The table lists various drugs, their associated therapeutic areas, biomarkers, labeling sections, and labeling text. The table also includes details about the date, number, and label version of the document. The table is updated on 12/2023.
**Boxed Warning**

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM**

**Hematologic Toxicity (Neutropenia and Thrombocytopenia)**

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [see Dosage and Administration (2.2)].

### 1 INDICATIONS AND USAGE

#### 1.2 Myelodysplastic Syndromes

REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

#### 6 ADVERSE REACTIONS

**6.1 Clinical Trials Experience**

Myelodysplastic Syndromes

A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 8 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 9 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease. [see Tables 9 and 10]

#### 8 USE IN SPECIFIC POPULATIONS

**8.5 Geriatric Use**

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. (…)

**14 CLINICAL STUDIES**

#### 14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality

The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1-risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. (…)

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<tbody>
<tr>
<td>217759, 03/24/2023</td>
<td>Leniolisib (1)</td>
<td>Pulmonary</td>
<td>PIK3CD</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES: The efficacy of JOENJA was evaluated in the placebo-controlled portion of Study 2201 (NCT02435173), a 12-week blinded, randomized, placebo-controlled study in adult and pediatric patients 12 years of age and older with confirmed APDS-associated genetic PI3Kδ mutation with a documented variant in either PIK3CD or PIK3R1. Baseline patient demographics are shown in Table 2. (…)</td>
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<tr>
<td>217759, 03/24/2023</td>
<td>Leniolisib (2)</td>
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<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES: The efficacy of JOENJA was evaluated in the placebo-controlled portion of Study 2201 (NCT02435173), a 12-week blinded, randomized, placebo-controlled study in adult and pediatric patients 12 years of age and older with confirmed APDS-associated genetic PI3Kδ mutation with a documented variant in either PIK3CD or PIK3R1. Baseline patient demographics are shown in Table 2. (…)</td>
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<tr>
<td>206947, 12/19/2021</td>
<td>Lenvatinib</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INICATIONS AND USAGE 1.4 Endometrial Carcinoma LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.4)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.</td>
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<tr>
<td>207988, 12/22/2015</td>
<td>Lesinurad</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.1 CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 inducers Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone), and in CYP2C9 poor metabolizers [see Clinical Pharmacology (12.3)]. (…)</td>
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<tr>
<td>020726, 04/05/2018</td>
<td>Letrozole</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INICATIONS AND USAGE 1.1 Adjuvant Treatment of Early Breast Cancer Femara (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.</td>
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<td>1.3 First and Second-Line Treatment of Advanced Breast Cancer Femara is indicated for local treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy [see Clinical Studies (14.4, 14.5)].</td>
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<td>6 ADVERSE REACTIONS 6.1 Adjuvant Treatment of Early Breast Cancer (…) Bone Study Results of a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%; P&lt;0.0001). (…)</td>
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| 021402, 08/30/2022                     | Levothyroxine | Endocrinology | Nonspecific (Congenital Hypothyroidism) | Indications and Usage, Warnings and Precautions, Use in Specific Populations | Lipid Study
In a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen. (…)

14 CLINICAL STUDIES
14.1 Updated Adjuvant Treatment of Early Breast Cancer
In a multicenter study enrolling over 8,000 postmenopausal women with resected, receptor-positive early breast cancer, one of the following treatments was randomly assigned in a double-blind manner (See Table 6) (…)

14.2 Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months
A double-blind, randomized, placebo-controlled trial of Femara was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease free prior to 5 years of adjuvant treatment with tamoxifen. (See Table 8) (…)

14.4 First-Line Treatment of Advanced Breast Cancer
A randomized, double-blind, multinational trial compared Femara 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIIB or loco-regional recurrences not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial. (See Table 11) (…)

14.5 Second-Line Treatment of Advanced Breast Cancer
Femara was initially studied at doses of 0.1 mg to 5.0 mg daily in six non-comparative Phase II/III trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least one antiestrogen therapy. (See Table 16) (…)

| 021451, 11/02/2018                        | Lisdioaine and Prilocaine (1) | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Methemoglobinemia
Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

| 021451, 11/02/2018                        | Lisdioaine and Prilocaine (2) | Anesthesiology | G6PD | Warnings and Precautions, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS
5.1 Methemoglobinemia
Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

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<td>G6PD</td>
<td>Warnings and Precautions</td>
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<td>5.1 Methemoglobinemia</td>
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|                                        |                               |                   |            |                   | Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 021623, 11/02/2018                     | Lidoceaine and Tetracaine (2) | Anesthesiology    | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions, Patient Counseling Information | 5 WARNINGS AND PRECAUTIONS |
|                                        |                               |                   |            |                   | 5.1 Methemoglobinemia |
|                                        |                               |                   |            |                   | Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue SYNERA and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. |
| 209229, 05/16/2018                     | Lofexidine                    | Anesthesiology    | CYP2D6     | Use in Specific Populations | 8 USE IN SPECIFIC POPULATIONS |
|                                        |                               |                   |            |                   | 8.8 CYP2D6 Poor Metabolizers |
|                                        |                               |                   |            |                   | Although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) (see Clinical Pharmacology (12.3)). |
| 203858, 12/20/2019                     | Lomitapide                   | Endocrinology     | Nonspecific (Homozygous Familial Hypercholesterolemia) | Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE |
|                                        |                               |                   |            |                   | 1.1 Homozygous Familial Hypercholesterolemia |
|                                        |                               |                   |            |                   | JUXTAPID is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDLC), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH). |
|                                        |                               |                   |            |                   | Limitations of Use |
|                                        |                               |                   |            |                   | • The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH). |
|                                        |                               |                   |            |                   | • The effect of JUXTAPID on cardiovascular mortality and mortality has not been determined. |
|                                        |                               |                   |            |                   | 5 WARNINGS AND PRECAUTIONS |
|                                        |                               |                   |            |                   | 5.1 Risk of Hepatotoxicity |
|                                        |                               |                   |            |                   | JUXTAPID can cause elevations in transaminases and hepatic steatosis, as described below (see Warnings and Precautions (5.2)). To what extent JUXTAPID-associated hepatic steatosis promotes the elevations in transaminases is unknown. Although cases of hepatic dysfunction (elevated transaminases with increase in bilirubin or INR) or hepatic failure have not been reported, there is concern that JUXTAPID could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of JUXTAPID in HoFH would have been unlikely to detect this adverse outcome given their size and duration (see Clinical Studies (14)). Elevation of Transaminases Elevation of transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) are associated with JUXTAPID. In the clinical trial, 10 (34%) of the 29 patients with HoFH had at least one elevation in ALT or AST ≥3×ULN, and 6 (14%) of the patients had at least one elevation in ALT or AST ≥5×ULN. There were no concomitant or subsequent clinically meaningful elevations in bilirubin, INR, or alkaline phosphatase (see Adverse Reactions (6.1)). During the 78-week HoFH clinical trial, no patients discontinued prematurely because of |

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Among the 19 patients who subsequently enrolled in the HoFH extension study, one discontinued due to increased transaminases that persisted despite several dose reductions, and one temporarily discontinued due to markedly elevated transaminases (ALT 24x ULN, AST 13x ULN) that had several possible causes, including a drug-drug interaction between JUXTAPID and the strong CYP3A4 inhibitor clarithromycin [see Drug Interactions (7.1)].

Hepatic Steatosis
JUXTAPID increases hepatic fat, with or without concomitant increases in transaminases. Hepatic steatosis is a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. The long-term consequences of hepatic steatosis associated with JUXTAPID treatment are unknown. During the HoFH clinical trial, the median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy (MRS) [see Adverse Reactions (6.1)]. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with JUXTAPID, but whether histological sequelae remain is unknown, especially after long-term use; protocol liver biopsies were not performed in the HoFH clinical trial. (…)

5.4 Reduced Absorption of Fat-Soluble Vitamins and Serum Fatty Acids
Given its mechanism of action in the small intestine, JUXTAPID may reduce the absorption of fat-soluble nutrients. In the HoFH clinical trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). In this trial, the median levels of serum vitamin E, ALA, linoleic acid, EPA, DHA, and arachidonic acid decreased from baseline to Week 26 but remained above the lower limit of the reference range. Adverse clinical consequences of these reductions were not observed with JUXTAPID treatment of up to 78 weeks. Patients treated with JUXTAPID should take daily supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA [see Dosage and Administration (2.1)]. Patients with chronic bowel or pancreatic diseases that predispose to malabsorption may be at increased risk for deficiencies in these nutrients with use of JUXTAPID.

5.5 Gastrointestinal Adverse Reactions
Gastrointestinal adverse reactions were reported by 27 (93%) of 29 patients in the HoFH clinical trial. Diarrhea occurred in 79% of patients, nausea in 65%, dyspepsia in 38%, and vomiting in 34%. Other reactions reported by at least 20% of patients include abdominal pain, abdominal discomfort, abdominal distension, constipation, and flatulence [see Adverse Reactions (6)]. Gastrointestinal adverse reactions of severe intensity were reported by 6 (21%) of 29 patients in the HoFH clinical trial, with the most common being diarrhea (4 patients, 14%); vomiting (3 patients, 10%); and abdominal pain, distension, and/or discomfort (2 patients, 7%). Gastrointestinal reactions contributed to the reasons for early discontinuation from the trial for 4 (14%) patients. (…)

5.6 Concomitant Use of CYP3A4 Inhibitors
CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with JUXTAPID is contraindicated [see Drug Interactions (7.1)]. In the JUXTAPID clinical trials, one patient with HoFH developed markedly elevated transaminases (ALT 24x ULN, AST 13x ULN) within 20 days of initiating the strong CYP3A4 inhibitor clarithromycin. If treatment with moderate or strong CYP3A4 inhibitors is unavoidable, JUXTAPID should be stopped during the course of treatment. (…)

5.7 Risk of Supratherapeutic or Subtherapeutic Anticoagulation with Warfarin
JUXTAPID increases the plasma concentrations of warfarin. Increases in the dose of JUXTAPID may lead to supratherapeutic anticoagulation, and decreases in the dose of JUXTAPID may lead to subtherapeutic anticoagulation. Difficulty controlling INR contributed to early discontinuation from the HoFH clinical trial for one of five patients taking concomitant warfarin. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in JUXTAPID dosage. The dose of warfarin should be adjusted as clinically indicated [see Drug Interactions (7.3)].

6 ADVERSE REACTIONS
One single-arm, open-label, 78-week trial has been conducted in 29 patients with HoFH, 23 of whom completed at least one year of treatment. The initial dosage of JUXTAPID was 5 mg daily, with titration up to 60 mg daily during an 18-week period based on safety and tolerability. In this trial, the mean age was 30.7 years (range, 18 to 65 years); 16 (55%) patients were men, 25 (86%) patients were Caucasian, 2 (7%) were Asian, 1 (3%) was African American, and 1 (3%) was multi-racial [see Clinical Studies (14)].

Five (17%) of the 28 patients with HoFH that participated in the clinical trial discontinued treatment due to an adverse reaction. The adverse reactions that contributed to treatment discontinuations included diarrhea (2 patients; 7%); and abdominal pain, nausea, gastroenteritis, weight loss, headache, and difficulty controlling INR on warfarin (1 patient each; 3%). The most common adverse reactions were gastrointestinal, reported by 27 (93%) of 29 patients. Adverse reactions reported by 28 (24%) patients in the HoFH clinical trial included diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. Other common adverse reactions, reported by 5 to 7 (17-24%) patients, included weight loss, abdominal discomfort, abdominal distension, constipation, flatulence, increased ALT, chest pain, influenza, nasopharyngitis, and fatigue. The adverse reactions reported in at least 10% of patients during the HoFH clinical trial are presented in Table 4. Adverse reactions of severe intensity were reported by 8 (28%) of 29 patients, with the most common being diarrhea (4 patients, 14%); vomiting (3 patients, 10%); increased ALT or hepatotoxicity (3 patients, 10%); and abdominal pain, distension, and/or discomfort (2 patients, 7%).

Transaminase Elevations
During the HoFH clinical trial, 10 (34%) of 29 patients had at least one elevation in ALT and/or AST ≥3x ULN (see Table 5). No clinically meaningful elevations in total bilirubin or alkaline phosphatase were observed. Transaminases typically fell within one to four weeks of reducing the dose or withdrawing JUXTAPID. Among the 19 patients who enrolled in an extension study following the HoFH clinical trial, one discontinued due to increased transaminases that persisted despite several dose reductions, and one temporarily discontinued due to markedly elevated transaminases (ALT 24x ULN, AST 13x ULN) that had several possible causes, including a drug-drug interaction between JUXTAPID and the strong CYP3A4 inhibitor clarithromycin [see Drug Interactions (7.1)].

Hepatic Steatosis
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| 213969, 11/20/2020                     | Lonafarnib (1) | Inborn Errors of Metabolism | LMNA | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies | ZOKINVY is indicated in patients 12 months of age and older with a body surface area (BSA) of 0.39 m² and above:  
  • To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)  
  • For the treatment of processing-deficient Progeroid Laminopathies with either:  
    o Heterozygous LMNA mutation with progerin-like protein accumulation  
    o Homozygous or compound heterozygous ZMPS1TE24 mutations  

  **Limitations of Use**  
  ZOKINVY is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Based upon its mechanism of action, ZOKINVY would not be expected to be effective in these populations.  

  **6 ADVERSE REACTIONS**  
  **6.1 Clinical Trial Experience**  
  The safety profile of ZOKINVY is based on 128 patient-years of treatment exposure (62 patients with HGPS and 1 patient with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation) and pooled results from two Phase 2 open-label, single-arm trials (n=63: 28 patients from Study 1 and 35 treatment naïve patients from Study 2). (…)  

  In these two studies, a total of 63 patients received ZOKINVY for a median duration of 2.2 years, with approximately 1.9 years at the recommended dose of 150 mg/m² twice daily. The population was 2 to 17 years old, with a similar proportion of males (33 [52%] patients) and females (30 [48%] patients). Most patients had classic HGPS (60 [95%] patients) compared to non-classic HGPS (2 [3%] patients) and 1 (2%) patient had Progeroid Laminopathy with LMNA heterozygous mutation. (…)  

  **8 USE IN SPECIFIC POPULATIONS**  
  **8.4 Pediatric Use**  
  The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPS1TE24 mutations) have been established in pediatric patients 2 years of age and older (see Clinical Studies [14]). The safety and effectiveness of ZOKINVY in pediatric patients less than 12 months of age have not been established.  

  **8.5 Adult Use**  
  The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPS1TE24 mutations) have been established in adults. Use of ZOKINVY in adults for these indications is based on adequate and well controlled studies in pediatric patients 2 years of age and older [see Clinical Studies (14)].  

  **14 CLINICAL STUDIES**  
  The efficacy of ZOKINVY is based on results from the Observational Cohort Survival Study, which retrospectively compared survival data from two Phase 2 studies in patients with HGPS to those from a natural history cohort. Study 1 (NCT00402436) was a Phase 2 open-label, single-arm trial that evaluated the efficacy of ZOKINVY in 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation with progerin-like protein accumulation). (…)  

| 213969, 11/20/2020 | Lonafarnib (2) | Inborn Errors of Metabolism | ZMPS1TE24 | Indications and Usage, Use in Specific Populations | ZOKINVY is indicated in patients 12 months of age and older with a body surface area (BSA) of 0.39 m² and above:  
  • To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)  
  • For the treatment of processing-deficient Progeroid Laminopathies with either:  
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  The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPS1TE24 mutations) have been established in adults. Use of ZOKINVY in adults for these indications is based on adequate and well controlled studies in pediatric patients 2 years of age and older [see Clinical Studies (14)].  

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</table>

#### 8.4 Pediatric Use

The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in pediatric patients ≥6 months of age with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in pediatric patients 6 months of age and older. Use of ZOKINVY for these indications is supported by adequate and well controlled studies in pediatric patients 6 months of age and older [see Clinical Studies (14)]. The safety and effectiveness of ZOKINVY in pediatric patients less than 6 months of age have not been established.

#### 8.6 Adult Use

The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in adults. Use of ZOKINVY in adults for these indications is based on adequate and well controlled studies in pediatric patients 6 months of age and older [see Clinical Studies (14)].

#### 6 ADVERSE REACTIONS

##### 6.1 Clinical Trials Experience

**Previously Untreated ALK-Positive Metastatic NSCLC (CROWN Study)**

The safety of LORBRENA was evaluated in 99 patients with ALK-positive NSCLC in a randomized, open-label, active-controlled trial for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who had not received previous systemic treatment for advanced disease [see Clinical Studies (14)]. The median duration of exposure to LORBRENA was 16.7 months (4 days to 34.3 months) and 76% received LORBRENA for at least 12 months.

**Previously Treated ALK-Positive Metastatic NSCLC**

The data described below reflect exposure to LORBRENA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA at least 100 mg orally once daily in Study B7461001, a multi-cohort, non-comparative trial [see Clinical Studies (14)]. The median duration of exposure to LORBRENA was 12.5 months (1 day to 35 months) and 52% received LORBRENA for ≥12 months. Patient characteristics were: median age of 53 years (19 to 85 years), age ≥65 years (18%), female (58%), White (49%), Asian (37%), and ECOG performance status 0 or 1 (96%).

**14 CLINICAL STUDIES**

**Previously Untreated ALK-Positive Metastatic NSCLC**

The efficacy of LORBRENA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was demonstrated in a nonrandomized, open-label, active-controlled, multicenter study (Study B7461001; NCT03052083). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. Neurologically stable patients with treated or untreated asymptomatic CNS metastases, including leptomeningeal metastases, were eligible. The efficacy of LORBRENA was demonstrated in a subgroup of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK kinase inhibitors who were enrolled in a non-randomized, dose-escalating and activity-estimating, multi-cohort, multicenter study (Study B7461001; NCT01970865). Patients included in this subgroup were required to have metastatic disease with at least 1 measurable target lesion according to RECIST v1.1, ECOG performance status 0 to 2, and documented ALK rearrangement in tumor tissue as determined by fluorescence in situ hybridization (FISH) assay or by Immunohistochemistry (IHC), and received LORBRENA 100 mg orally once daily. Patients with asymptomatic CNS metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were eligible. Patients with severe, acute, or chronic psychiatric conditions including suicidal ideation or behavior were excluded. In addition, for patients with ALK-negative metastatic NSCLC, the extent and type of prior treatment was specified for each individual cohort (see Table 5).

##### 6 ADVERSE REACTIONS

**6.1 Clinical Trials Experience**

**Previously Treated ALK-Positive Metastatic NSCLC**

The efficacy of LORBRENA was evaluated in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA at least 100 mg orally once daily in Study B7461001, a multi-cohort, non-comparative trial [see Clinical Studies (14)]. The median duration of exposure to LORBRENA was 12.5 months (1 day to 35 months) and 52% received LORBRENA for ≥12 months. Patient characteristics were: median age of 53 years (19 to 85 years), age ≥65 years (18%), female (58%), White (49%), Asian (37%), and ECOG performance status 0 or 1 (96%).

**ZOKINVY in adults for these indications is based on adequate and well controlled studies in pediatric patients ≥2 years of age [see Clinical Pharmacology (12.1), Clinical Studies (14)]**

**8.4 Pediatric Use**

The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in pediatric patients ≥6 months of age with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in pediatric patients 6 months of age and older. Use of ZOKINVY for these indications is supported by adequate and well controlled studies in pediatric patients 6 months of age and older [see Clinical Studies (14)]. The safety and effectiveness of ZOKINVY in pediatric patients less than 6 months of age have not been established.

**8.6 Adult Use**

The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in adults. Use of ZOKINVY in adults for these indications is based on adequate and well controlled studies in pediatric patients 6 months of age and older [see Clinical Studies (14)].

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<td>Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trials Experience</td>
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<td>The data reflect placebo-controlled and open-label clinical studies in 77 patients with PH1 (including 56 pediatric patients). Patients ranged in age from 4 months to 61 years at first dose. The median duration of exposure was 9.1 months (range 1.9 to 21.7 months). Overall, 58 patients were treated for at least 6 months, and 16 patients for at least 12 months. In the randomized, placebo-controlled, double-blind study ILLUMINATE-A in pediatric and adult patients with PH1 aged 6 to 61 years, 26 patients received OXLUMO and 13 patients received placebo. Of these, 25 patients received ≥5 months of treatment. (…) In the single-arm study (ILLUMINATE-B) in patients with PH1 who are &gt;6 years of age, the safety profile observed was similar to that seen in ILLUMINATE-A [see Clinical Studies (14)].</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.4 Pediatric Use</td>
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<td>The safety and effectiveness of OXLUMO have been established in pediatric patients aged birth and older. Use of OXLUMO in these age groups is supported by evidence from an adequate and well controlled study of OXLUMO in children 6 years or older and adults with PH1 (ILLUMINATE-A), and a single-arm clinical study in children less than 6 years of age with PH1 (ILLUMINATE-B) [see Adverse Reactions (6.1), Clinical Studies (14)].</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics</td>
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<td>The pharmacodynamic effects of OXLUMO have been evaluated in adult and pediatric patients with PH1 across a range of doses and dosing frequency. Dose-dependent reductions in urinary oxalate levels were observed, resulting in the selection of the recommended body weight-based loading and maintenance dosing regimens. With the recommended dosing regimens, onset of effect was observed within two weeks after the first dose and maximal reductions in urinary oxalate were observed by Month 2 and persisted with continued use of OXLUMO maintenance dosage [see Figures 1 and 2 in Clinical Studies (14.1, 14.2).]</td>
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<td>12.3 Pharmacokinetics</td>
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<td>The pharmacokinetic (PK) properties of OXLUMO were evaluated following administration of single and multiple dosages in patients with PH1 as summarized in Table 3. (See Table 3)</td>
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<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.1 ILLUMINATE-A</td>
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<td>ILLUMINATE-A was a randomized, double-blind trial comparing lusutamir and placebo in 39 patients 6 years of age and older with PH1 and an eGFR ≥30 mL/min/1.73 m² (ILLUMINATE-A; NCT03881184). Patients received 3 loading doses of 3 mg/kg OXLUMO (N=26) or placebo (N=13) administered once monthly, followed by quarterly maintenance doses of 3 mg/kg OXLUMO or placebo [see Dosage and Administration (2.1)]. (…)</td>
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<td>14.2 ILLUMINATE-B</td>
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<td>ILLUMINATE-B was a single-arm study in 18 patients &gt;45 mL/min/1.73 m² for patients ≥12 months of age or a normal serum creatinine for patients &lt;12 months of age (ILLUMINATE-B; NCT03905694). Efficacy analyses included the first 16 patients who received 6 months of treatment with OXLUMO. Dosing was based on body weight [see Dosage and Administration (2.1)]. (…)</td>
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<td>14.3 Pediatric Use</td>
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<td>14.4 Other Uses</td>
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<td>210923, 07/31/2018</td>
<td>Lusutrombopag (4)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.</td>
</tr>
<tr>
<td>210923, 07/31/2018</td>
<td>Lusutrombopag (5)</td>
<td>Hematology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.</td>
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<tr>
<td>208700, 05/29/2020</td>
<td>LuTate Octetate</td>
<td>Oncology</td>
<td>SSTR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE LUTATHERA is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience The data in Warnings and Precautions reflect exposure to LUTATHERA in 111 patients with advanced, progressive midgut neuroendocrine tumors (NETTER-1). Safety data in Warnings and Precautions were also obtained in an additional 22 patients in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor-positive tumors enrolled in ERASMUS (see Clinical Studies (14.1)). Patients with progressive, somatostatin receptor-positive midgut carcinoid tumors to receive LUTATHERA 7.4 GBq (200 mCi) administered every 8 to 16 weeks concurrently with the recommended amino acid solution and with long-acting octreotide (30 mg administered by intramuscular injection within 24 hours of each LUTATHERA dose) (n = 111), or high-dose octreotide (defined as long-acting octreotide 60 mg by intramuscular injection every 4 weeks) (n = 112) [see Clinical Studies (14.1)]. (…) ERASMUS Safety data are available from 1214 patients in ERASMUS, an international, singleinstitution, single-arm, open-label trial of patients with somatostatin receptor-positive tumors (neuroendocrine and other primaries). Patients received LUTATHERA 7.4 GBq (200 mCi) administered every 6 to 13 weeks with or without octreotide. (…).</td>
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<tr>
<td>215833, 03/23/2022</td>
<td><strong>cmkb (1)</strong> Oncology</td>
<td>FOLH1 (PSMA)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td><strong>MARGENZA is indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HR2 regimens, at least one of which was for metastatic disease [see Dosage and Administration (2.1) and Clinical Studies (14.1)].</strong></td>
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</tr>
<tr>
<td>09/29/2021</td>
<td><strong>cmkb (1)</strong> Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td><strong>WARNINGs</strong> Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate.</td>
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<tr>
<td>214662, 09/29/2021</td>
<td><strong>Mafexibat</strong> Gastroenterology</td>
<td>JAG1</td>
<td>Clinical Studies</td>
<td><strong>14 CLINICAL STUDIES</strong> The efficacy of LIVMARLI was evaluated in Trial 1 (NCT02160782), which consisted of a 18-week open-label treatment period; a 4-week randomized, double-blind, placebo-controlled drug-withdrawal period; a subsequent 26-week open-label treatment period; and a long-term open-label extension period. Thirty-one pediatric ALGS patients with cholestasis and pruritus were enrolled, with 90.3% of patients receiving at least one medication to treat pruritus at study entry. All patients had JAGGED1 mutation.</td>
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<tr>
<td>761150, 12/16/2020</td>
<td><strong>Margetuximab-cmkb (1)</strong> Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td><strong>14 CLINICAL PHARMACOLOGY</strong> 12.3 Pharmacokinetics Following the approved recommended dosage, the steady-state geometric mean (% CV) Cmax of margetuximab-cmkb is 466 (20%) µg/mL and AUC0-21d is 4120 (27%) µg.day/mL in patients with HER2-positive relapsed or refractory advanced breast cancer. Specific Populations N6 clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), sex, race (Caucasian, Black, Asian), mbd to moderate (CLR 30 to 89 mL/min estimated using the Cockcroft-Gault equation) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST &gt; ULN, or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2), number of prior chemotherapy (cisplatin, gemcitabine, eribulin, and vinorelbine). The effect of severe renal impairment (CLR &lt; 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
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<tr>
<td>06/05/1998</td>
<td><strong>Lutetium Lu 177 Vipivotide</strong> Tetraxetan</td>
<td>Oncology</td>
<td>FOLH1 (PSMA)</td>
<td><strong>INDICATIONS AND USAGE</strong> PLUVICTO is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. <strong>2 DOSAGE AND ADMINISTRATION</strong> 2.2 Patient Selection Select patients with previously treated mCRPC for treatment with PLUVICTO using LOCAMETZ or another approved PSMA-11 imaging agent based on PSMA expression in tumors. Additional selection criteria were used in the VISION study [see Clinical Studies (14)]. Refer to the prescribing information for the PSMA imaging agent.</td>
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<tr>
<td>215833, 03/23/2022</td>
<td><strong>Mafenide Acetate</strong> Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate.</td>
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<tr>
<td>09/29/2021</td>
<td><strong>Mafenide Acetate</strong> Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td><strong>Mafenide Acetate</strong> was reported following therapy with mafenide acetate.</td>
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<td>Margetuximab-cmkb (2)</td>
<td>Oncology</td>
<td>FCGR2A (CD32A)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  Specific Populations  No clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), sex, race (Caucasian, Black, Asian), mild to moderate (CLcr 30 to 89 mL/min estimated using the Cockcroft-Gault equation) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST &gt; ULN, or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (44 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2) or concurrent chemotherapies (cetuximab, gemcitabine, eribulin and vinorelbine). The effect of severe renal impairment (CLcr &lt; 15 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
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<td>761150, 12/16/2020</td>
<td>Margetuximab-cmkb (3)</td>
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<td>FCGR2B (CD32B)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  Specific Populations  No clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), sex, race (Caucasian, Black, Asian), mild to moderate (CLcr 30 to 89 mL/min estimated using the Cockcroft-Gault equation) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST &gt; ULN, or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2) or concurrent chemotherapies (cetuximab, gemcitabine, eribulin and vinorelbine). The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
</tr>
<tr>
<td>761150, 12/16/2020</td>
<td>Margetuximab-cmkb (4)</td>
<td>Oncology</td>
<td>FCGR3A (CD16A)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  Specific Populations  No clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), sex, race (Caucasian, Black, Asian), mild to moderate (CLcr 30 to 89 mL/min estimated using the Cockcroft-Gault equation) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST &gt; ULN, or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2) or concurrent chemotherapies (cetuximab, gemcitabine, eribulin and vinorelbine). The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
</tr>
<tr>
<td>214998, 04/28/2022</td>
<td>Mavacamten</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>2. DOSAGE AND ADMINISTRATION 2.1. Initiation, Maintenance, and Interruption of Treatment  Confirm absence of pregnancy and usage of effective contraception in females of reproductive potential [see Warnings and Precautions (5.4)]. Initiation or up-titration of CAMZYOS in patients with LVEF &lt;55% is not recommended. The recommended starting dose is 5 mg once daily without regard to food; allowable subsequent doses with titration are 2.5, 5, 10, or 15 mg once daily. Patients may develop heart failure symptoms with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
</tr>
</tbody>
</table>

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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tr>
<td>12/2023</td>
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<tr>
<td>012250, 11/02/2018</td>
<td>Mepivacaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td></td>
<td>WARNINGS Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>012250, 11/02/2018</td>
<td>Mepivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td></td>
<td>WARNINGS Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>125526, 03/08/2023</td>
<td>Meloprolizumab</td>
<td>Oncology</td>
<td>FIP1L1/PDGFRα (Congenital FIP1L1/PDGFRα)</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
<td>6.4 Clinical Trials Experience in Hypereosinophilic Syndrome: A total of 108 adult and adolescent patients aged 12 years and older with HES were evaluated in a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients with non-hematologic secondary HES or FIP1L1/PDGFRα kinase-positive HES were excluded from the trial. (…)</td>
</tr>
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| 205919, 04/29/2020                | Mercaptopurine | Oncology | TPMT | Dosage and Administration, Warnings and Precautions, | The recommended starting dose of PURIXAN in multi-agent combination chemotherapy maintenance regimens is 1.5 to 2.5 mg/kg (50 to 75 mg/m²) as a single daily dose. After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cellularity. Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression. Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]. Homozygous deficiency in either TPMT or NUDT15 Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Heterozygous deficiency in TPMT and/or NUDT15 Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. 5 WARNINGS AND PRECAUTIONS 5.1 Myelosuppression The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia. Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)]. Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by coadministration with drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)]. 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percent of the planned dosage) was as follows: homozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percent of the planned dosage) was as follows: homozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2* and *3* alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression. * Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.
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<tbody>
<tr>
<td>204630, 05/21/2018</td>
<td>Methylene Blue</td>
<td>Hematology</td>
<td>G6PD</td>
<td>Contraindications, Warnings and Precautions</td>
<td>4 CONTRAINDICATIONS PROVAYBLUE™ is contraindicated in the following conditions: • Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)]. • Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia [see Warnings and Precautions (5.3, 5.4)].</td>
</tr>
</tbody>
</table>

2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)].

| Homozygous deficiency in either TPMT or NUDT15 |
| Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. |
| Heterozygous deficiency in TPMT and/or NUDT15 |
| Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. |

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia.

Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)].

Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity.

Myelosuppression can be exacerbated by concomitant drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)].

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TMPT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT2, TPMT3A, and TPMT3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the "2 and 3 alleles") is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient’s actual TPMT activity [see Dosage and Administration (2.2) and Warnings and Precautions (5.1)].

5.3 Lack of Effectiveness

Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to aryl amines such as aniline or sulfa drugs such as dapson. Monitor response to therapy with PROVAYBLUE™ through resolution of methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a response, consider additional treatment options [see Dosage and Administration (2.2)].

Patients with glucose-6-phosphate dehydrogenase deficiency may not reduce PROVAYBLUE™ to its active form in vivo. PROVAYBLUE™ may not be effective in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

5.4 Hemolytic Anemia

Hemolysis can occur during treatment of methemoglobinemia with PROVAYBLUE™. Laboratory testing may show Heinz bodies, elevated indirect bilirubin and low haptoglobin, but the Coombs test is negative. The onset of anemia may be delayed 1 or more days after treatment with PROVAYBLUE™. The anemia may require red blood cell transfusions. [see Adverse Reactions (6.1)]. Use the lowest effective number of doses of PROVAYBLUE™ to treat methemoglobinemia. Discontinue PROVAYBLUE™ and consider alternative treatments of methemoglobinemia if severe hemolysis occurs.

Treatment of patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency with PROVAYBLUE™ may result in severe hemolysis and severe anemia. PROVAYBLUE™ is contraindicated for use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency [see Contraindications (4)].

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<td>017854, 08/29/2017</td>
<td>Metoclopramide</td>
<td>Gastroenterology</td>
<td>CYB5R</td>
<td>Use in Specific Populations</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.8 NADH-Cytochrome b5 Reductase Deficiency</td>
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<td>Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal [see Overdosage (10)].</td>
</tr>
<tr>
<td>017854, 08/29/2017</td>
<td>Metoclopramide</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Use in Specific Populations, Overdosage</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal [see Overdosage (10)].</td>
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<td>017854, 08/29/2017</td>
<td>Metoclopramide</td>
<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.2 Dosage for Gastroesophageal Reflux</td>
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<td>Reglan tablets may be administered continuously or intermittently in patients with symptomatic gastroesophageal reflux who fail to respond to conventional therapy: Continuous Dosing</td>
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<td>The recommended adult dosage of Reglan is 10 to 15 mg four times daily for 4 to 12 weeks. The treatment duration is determined by endoscopic response. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 60 mg.</td>
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<td>Table 1 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 1)</td>
</tr>
<tr>
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<td>2.3 Dosage for Acute and Recurrent Diabetic Gastroesophagus</td>
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<td>The recommended adult dosage for the treatment of acute and recurrent diabetic gastroesophagus is 10 mg four times daily for 2 to 8 weeks, depending on symptomatic response. Avoid Reglan treatment for greater than 12 weeks [see Warnings and Precautions (5.1)]. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 40 mg.</td>
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<td>Table 2 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 2)</td>
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<td>019962, 06/01/2022</td>
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<td>Cardiology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td></td>
<td>Elimination</td>
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<td>Metabolism: Metoprolol undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monodeethylmetoprolol is a major oxidative metabolite, is formed primarily by CYP2D6, an enzyme subject to genetic variability (see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.9)).</td>
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<tr>
<td>125390, 02/28/2022</td>
<td>Metolectin</td>
<td>Endocrinology</td>
<td>LEP</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS</td>
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<td>4.1 General Obesity</td>
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<tr>
<td>207997, 03/04/2020</td>
<td>Midostaurin (1)</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency. MYALEPT has not been shown to be effective in treating general obesity, and the development of anti-metreleptin antibodies with neutralizing activity has been reported in obese patients treated with MYALEPT [see Warnings and Precautions (5.1)].</td>
</tr>
<tr>
<td>207997, 03/04/2020</td>
<td>Midostaurin (2)</td>
<td>Oncology</td>
<td>NPM1</td>
<td>Clinical Studies</td>
<td>(2) Of the 563 patients with NPM1 testing, 58% had an NPM1 mutation. The two treatment groups were generally balanced with respect to the baseline demographics and disease characteristics, except that the placebo arm had a higher percentage of females (59%) than in the midostaurin arm (52%). NPM1 mutations were identified in 55% of patients tested on the midostaurin arm and 60% of patients tested on the placebo arm. (…).</td>
</tr>
<tr>
<td>207997, 03/04/2020</td>
<td>Midostaurin (3)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Clinical Studies</td>
<td>(2) Of the 116 patients treated, a study steering committee identified 89 patients who had measurable C-findings and were evaluable for response. The median age in this group was 64 years (range: 25 to 82), 64% of patients were male, and nearly all patients (97%) were Caucasian. Among these patients, 36% had prior therapy for SM, and 82% had the KIT D816V mutation detected at baseline. Their median duration of treatment was 11 months (range: &lt; 1 to 68 months), with treatment ongoing in 17%. Efficacy was established on the basis of confirmed complete remission (CR) plus incomplete remission (ICR) by 6 cycles of RYDAPT by modified Valent criteria. Confirmed major or partial responses occurred in 46 of 73 patients with a documented KIT D816V mutation, 7 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. (…).</td>
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<tr>
<td>208623, 08/10/2018</td>
<td>Migalastat</td>
<td>Inborn Errors of Metabolism</td>
<td>GLA</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>GALAFOLD™ is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data [see Clinical Pharmacology (12.1)]. (…).</td>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tr>
<td>202611, 04/27/2018</td>
<td>Mirabegron</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action In Vitro Amaneability Assay In an in vitro assay (HEK-293 assay), Human Embryonic Kidney (HEK-293) cell lines were transfected with specific GLA variants (mutations) which produced mutant alpha-Gal A proteins. In the transfected cells, amanenability of the GLA variants was assessed after a 5-day incubation with 10 micromol/L migalastat. A GLA variant was categorized as amenable if the resultant mutant alpha-Gal A activity (measured in the cell lysates) met two criteria: 1) it showed a relative increase of at least 20% compared to the pre-treatment alpha-Gal A activity, and 2) it showed an absolute increase at least 3% of the wild-type (normal) alpha-Gal A activity. The in vitro assay did not evaluate trafficking of the mutant alpha-Gal A proteins into the lysosome or the dissociation of migalastat from the mutant alpha-Gal A proteins within the lysosome. Also, the in vitro assay did not test whether a GLA variant causes Fabry disease or not. The GLA variants which are amenable to treatment with GALAFOLD, based on the in vitro assay data, are shown in Table 2. Inclusion of GLA variants in this table does not reflect interpretation of their clinical significance in Fabry disease. Whether a certain amenable GLA variant in a patient with Fabry disease is disease-causing or not should be determined by the prescribing physician (in consultation with a clinical genetics professional, if needed) prior to treatment initiation. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease). (See Table 2) If a GLA variant does not appear in Table 2, it is either non-amenable (if tested) or has not been tested for in vitro amanenability. For further information, please contact Amicus Medical Information at 1-877-4AMICUS or <a href="mailto:medinfousa@amicusrx.com">medinfousa@amicusrx.com</a>. 12.2 Pharmacodynamics In Study 1, 31 of 50 patients with amenable GLA variants (18 on GALAFOLD, 13 on placebo) had lyso-Gb3 assessments available after 6 months of treatment. (...) In Study 2, 46 of 56 patients with amenable GLA variants (31 on GALAFOLD, 15 on enzyme replacement therapy (ERT)) had lyso-Gb3 assessments available after 18 months of treatment. The median change from baseline to month 18 in plasma lyso-Gb3 (nmol/L) was 0.53 (range -2.27, 28.3) in patients on GALAFOLD and -0.03 (range -11.9, 2.57) in patients on ERT. 14 CLINICAL STUDIES (...) Of the 67 enrolled patients, 50 patients (32 females, 18 males) had amenable GLA variants based on the in vitro amanenability assay [see Clinical Pharmacology (12.1)]. (See Table 3) In Study 1, patients with non-amenable GLA variants (n = 17) had no change from baseline in the average number of GL-3 inclusions per KIC after 6 months of treatment.</td>
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<tr>
<td>761310, 11/14/2022</td>
<td>Mirvetuximab</td>
<td>Oncology</td>
<td>FOLR1</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies 1 INDICATIONS AND USAGE ELAHERE™ is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinumresistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test [see Dosage and Administration (2.1)]. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer with ELAHERE based on the presence of FRα tumor expression [see Indications &amp; Usage (1) and Clinical Studies (14)] using an FDA-approved test. Information on FDA-approved tests for the measurement of FRα tumor expression is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 14 CLINICAL STUDIES The efficacy of ELAHERE was evaluated in Study 0417 (NCT04296890), a single-arm trial of patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (n=106). Patients were permitted to receive up to three prior lines of systemic therapy. All patients were required to have received prior bevacizumab. The trial enrolled patients whose tumors were positive for FRα expression as determined by the VENTANA FOLR1 (FOLR1- 2.1) RxDx Assay.</td>
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<tr>
<td>216196, 02/17/2022</td>
<td>Mitapivat</td>
<td>Hematology</td>
<td>PKLR</td>
<td>Clinical Studies 14 CLINICAL STUDIES Patients with PK Deficiency Patients Not Regularly Transfused</td>
<td></td>
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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.
The efficacy of PYRUKYND was evaluated in ACTIVATE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT03548220) of 80 adults with PK deficiency who were not regularly transfused, defined as having had no more than 4 transfusions in the 52-week period prior to treatment and no transfusions in the 3-month period prior to treatment. Patients were included if they had documented presence of at least 2 variant alleles in the pyruvate kinase liver and red blood cell (PKLR) gene, of which at least 1 was a missense variant, and HB less than or equal to 10 g/dL. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded because these patients did not achieve HB response (change from baseline in HB ≥1.5 g/dL at ≥50% assessments) in the dose-ranging study. Randomization was stratified by average screening HB (<8.5 vs ≥8.5 g/dL) and PKLR gene variant category (missense/missense vs. missense/non-missense). The median duration of treatment with PYRUKYND was 24.1 weeks (range 23.6 to 27.4 weeks). Overall, 30 (75%) patients were exposed to PYRUKYND for >24 weeks and ≥26 weeks. Among the 80 randomized patients, the median age was 33 years (range 18 to 76) and 40% were male; race was reported in 86% of patients: 75% were White, 10% Asian, 1.3% Native Hawaiian/Other Pacific Islander and 1.3% were other races. The median baseline hemoglobin was 8.5 g/dL (range 6.4 to 10.2 g/dL). There were 53 patients (66%) with the missense/pseudokinase PKLR gene variant category, and 25 patients (31%) with the missense/non-missense PKLR gene variant category. There were 58 patients (73%) who had a history of splenectomy. Patients who were regularly transfused were evaluated in ACTIVATE-T, a multinational single-arm clinical trial (NCT03556699) of 27 adults with PK deficiency who had a minimum of 6 transfusion episodes in the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 variant alleles in the PKLR gene (of which at least 1 was a missense variant). Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded. Following a period of dose titration up to 50 mg twice daily, patients continued on a fixed dose of PYRUKYND for 24 weeks. The median duration of treatment with PYRUKYND was 40.3 weeks (range 16.3 to 46.3 weeks). Overall, 20 (74%) patients were exposed to PYRUKYND for >40 weeks and ≥47 weeks. The median age was 33 years (range 18 to 66) and 28% were male; race was reported in 85% of patients: 74% were White and 11% Asian. The median baseline hemoglobin was 9.1 g/dL (range 7.4 to 10.9 g/dL). Patients had a median of 9 transfusion episodes (range 6 to 17 episodes) in the 52 weeks before the first dose of study treatment and a median of 7 red blood cell units transfused (range 3 to 20 units) standardized to 24 weeks. There were 20 patients (74%) with the missense/pseudokinase PKLR gene variant category, and 7 patients (26%) with the missense/non-missense PKLR gene variant category. The efficacy of PYRUKYND in patients with PK deficiency who were regularly transfused was evaluated in ACTIVATE-T, a multinational single-arm clinical trial (NCT03556699) of 27 adults with PK deficiency who had a minimum of 6 transfusion episodes in the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 variant alleles in the PKLR gene (of which at least 1 was a missense variant). Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded. Following a period of dose titration up to 50 mg twice daily, patients continued on a fixed dose of PYRUKYND for 24 weeks. The median duration of treatment with PYRUKYND was 40.3 weeks (range 16.3 to 46.3 weeks). Overall, 20 (74%) patients were exposed to PYRUKYND for >40 weeks and ≥47 weeks. The median age was 33 years (range 18 to 66) and 28% were male; race was reported in 85% of patients: 74% were White and 11% Asian. The median baseline hemoglobin was 9.1 g/dL (range 7.4 to 10.9 g/dL). Patients had a median of 9 transfusion episodes (range 6 to 17 episodes) in the 52 weeks before the first dose of study treatment and a median of 7 red blood cell units transfused (range 3 to 20 units) standardized to 24 weeks. There were 20 patients (74%) with the missense/pseudokinase PKLR gene variant category, and 7 patients (26%) with the missense/non-missense PKLR gene variant category.

**PRECAUTIONS**

**Reduced Plasma Cholinesterase Activity**

The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiophate, and certain antiasthmatic drugs). MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.1 to 0.2 mg/kg MIVACRON, the clinically effective duration of action was 8 minutes to 11 minutes longer in patients heterozygous for the atypical plasma cholinesterase gene than in genotypically normal patients. As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (one in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In these such adults, patients, a small dose of 0.03 mg/kg (approximately the ED10-20 in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with complete neuromuscular block using pyridostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

Administration of MIVACRON over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see PRECAUTIONS - Reduced Plasma Cholinesterase Activity and CLINICAL PHARMACOLOGY - Individualization of Dosages subsection).

**Individualization of Dosages**

**Reduced Plasma Cholinesterase Activity**

The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>020098, 07/26/2018</td>
<td>Anesthesiology</td>
<td>BCHE</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
<td>Warnings Administration MIVACRON is metabolized by plasma cholinesterase and should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.</td>
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<tr>
<td>215310, 09/15/2021</td>
<td>Mobocertinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: EXXIVITY is indicated for the treatment of adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)], whose disease has progressed on or after platinum-based chemotherapy.</td>
</tr>
<tr>
<td>020717, 01/15/2015</td>
<td>Modafinil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY: 12.3 Pharmacokinetics: Interactions with CNS Active Drugs: CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine and desipramine) and selective serotonin reuptake inhibitors that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased.</td>
</tr>
<tr>
<td>050791, 10/27/2015</td>
<td>Mycophenolic Acid</td>
<td>Transplantation</td>
<td>HPRT1</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS: 5.10 Rare Hereditary Deficiencies: Myofrictic is an insome monophosphate dehydrogenase inhibitor (IMPDH Inhibitor). Myofrictic should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease including renal failure.</td>
</tr>
<tr>
<td>014214, 11/28/2012</td>
<td>Nalidixic Acid</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS: Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS)</td>
</tr>
<tr>
<td>021204, 10/28/2021</td>
<td>Nateglinide</td>
<td>Endocrinology</td>
<td>CYP2C9</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS: Drugs That May Increase the Blood-Glucose-Lowering Effect of STARLIX and Susceptibility to Hypoglycemia: Nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents, anabolic hormones (e.g., methandrostanolone), guanethidine, gynema sylvestre, glucocorticoids, and inhibitors of CYP2C9 (e.g., amiodarone, fluconazole, voriconazole, sulfinpyrazone) or in patients known to be poor metabolizers of CYP2C9 substrates, alcohol.</td>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
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</table>
| 021742, 11/30/2017                     | Nebivolol | Cardiology | CYP2D6 | Dosage and Administration, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION 2.2 Subpopulations CYP2D6 Polymorphism
No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers [see Clinical Pharmacology (12.3)]. |
| 215842, 09/29/2023                     | Nedosiran | Nephrology | AGXT | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
RIVFLOZA is indicated to lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., eGFR ≥ 30 mL/min/1.73 m² [see Clinical Pharmacology (12.3)], Clinical Studies (14.1)]. |

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<td>Infectious Diseases</td>
<td>MT-RNR1</td>
<td>Warnings</td>
<td>Precautions Cardiovascular-Active Drugs Digoxin</td>
</tr>
<tr>
<td>Neratinib (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Advanced Adjuvant Treatment of Early-Stage Breast Cancer NERLYNX as a single agent is indicated for the advanced adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer, to follow adjuvant trastuzumab based therapy [see Clinical Studies (14.1)]. 1.2 Advanced or Metastatic Breast Cancer NERLYNX in combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting [see Clinical Studies (14.2)]. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Extended Adjuvant Treatment of Early Stage Breast Cancer ExteNET The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. (…) Advanced or Metastatic Breast Cancer NALA The data described below reflect the safety data of NERLYNX plus capecitabine in NALA, a randomized, multicenter, multinational, open-label, active-controlled study of HER2+ metastatic breast cancer in patients, with or without brain metastases, who have received two or more prior anti HER2-based regimens in the metastatic setting. (…)</td>
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<td>Neratinib (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>The CONTROL (NCT02400476) study was a multicenter, open-label, multi-cohort trial evaluating patients with early stage HER2-positive breast cancer treated with neratinib 240 mg daily for up to one year receiving loperamide prophylaxis with and without an additional anti-diarrheal treatment. (…)</td>
</tr>
</tbody>
</table>
| 020851, 02/25/2020                     | Neratinib (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES
14.1 Extended Adjuvant Treatment of Early Stage Breast Cancer
The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer. A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). Randomization was stratified by the following factors: hormone receptor status, nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. (…) Fifty-seven percent (57%) had hormone receptor positive disease (defined as ER-positive and/or PgR-positive), 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. (See Table 12) (…). HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment. HER2 positivity was defined as a HER2 immunohistochemistry (IHC) score of 3+ or IHC 2+ with confirmatory in situ hybridization (ISH) positive. Fifty-nine percent of these patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). 69% had received two prior anti-HER2 based regimens, 31% had received three or more prior anti-HER2 based regimens, 81% had visceral disease, and 19% had non-visceral-only disease. Patients with asymptomatic or stable brain metastases were included in NALA trial (16%). (See Table 14) (…). |
| 022068, 09/25/2019                     | Nilotinib (1) | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Adult and Pediatric Patients with Newly Diagnosed Ph+ CML-CP
Tasigna (nilotinib) is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. 1.2 Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
Tasigna is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib. 1.3 Pediatric Patients with Resistant or Intolerant Ph+ CML-CP
Tasigna is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy. |
| 020851, 02/25/2020                     | Neratinib (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
Dosing in Adult Patients with Newly Diagnosed Ph+ CML-CP
The recommended dose of Tasigna is 300 mg orally twice daily. Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
The recommended dose of Tasigna is 400 mg orally twice daily. Dosage in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP
The recommended dose of Tasigna for pediatric patients is 230 mg/m2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs. 2.2 Discontinuation of treatment after a sustained molecular response (MR4.5) on Tasigna
Patient Selection
Eligibility for Discontinuation of Treatment
Ph+ CML-CP patients with typical BCR-ABL transcripts who have been taking Tasigna for a minimum of 3 years and have achieved a sustained molecular response (MR4.5, corresponding to ≤ BCR-ABL/ABL ≤ 0.0002% IS) may be eligible for treatment discontinuation [see Clinical Studies (14.3, 14.4)]. Information on FDA authorized tests for the detection and quantitation of BCR-ABL transcripts to determine eligibility for treatment discontinuation is available at http://www.fda.gov/Drugs/InformationOnFDAApprovedTests/ApprovedTests/ucm070427.htm. |

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Patients with typical BCR-ABL transcripts (i.e., 13a2/b2a2 or e14a2/b3a2) who achieve the sustained MR4.5 criteria are eligible for discontinuation of Tasigna treatment. Patients must continue to be monitored for possible loss of molecular remission after treatment discontinuation. Use the same FDA authorized test to consistently monitor molecular response levels while on and off treatment.

Consider discontinuation of treatment in patients with newly diagnosed Ph+ CML-CP who have:

- been treated with Tasigna for at least 3 years
- maintained a molecular response of at least MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01% IS) for one year prior to discontinuation of therapy
- achieved an MR4.5 for the last assessment taken immediately prior to discontinuation of therapy
- been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
- no history of accelerated phase or blast crisis
- no history of prior attempts of treatment-free remission discontinuation that resulted in relapse

Consider discontinuation of treatment in patients with Ph+ CML-CP that are resistant or intolerant to treatment with imatinib who have achieved a sustained molecular response (MR4.5) on Tasigna who have:

- been treated with Tasigna for a minimum of 3 years
- been treated with imatinib only prior to treatment with Tasigna
- achieved a molecular response of MR4.5 (corresponding to = BCR-ABL/ABL ≤ 0.0032% IS)
- sustained an MR4.5 for a minimum of one year immediately prior to discontinuation of therapy
- been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
- no history of accelerated phase or blast crisis
- no history of prior attempts of treatment-free remission discontinuation that resulted in relapse.

Monitor BCR-ABL transcript levels and complete blood count with differential in patients who have discontinued Tasigna therapy monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter (see Warnings and Precautions (5.16)).

Upon the loss of MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01% IS) during the treatment-free phase, monitor BCR-ABL transcript levels every 2 weeks until BCR-ABL levels remain lower than major molecular response (MRM, corresponding to MR3.0 or = BCR-ABL/ABL ≤ 0.1% IS) for 4 consecutive measurements. The patient can then proceed to the original monitoring schedule.

2.3 Reinitiation of treatment in patients who lose molecular response after discontinuation of therapy with Tasigna.

- Newly diagnosed patients who lose MMR must reinitiate treatment within 4 weeks at the dose level prior to discontinuation of therapy (see Warnings and Precautions (5.16)). Patients who reinitiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until major molecular response is re-established and every 12 weeks thereafter.
- Patients resistant or intolerant to prior treatment that included imatinib with confirmed loss of MR4.0 (2 consecutive measures separated by at least 4 weeks showing loss of MMR) or loss of MMR must reinitiate treatment within 4 weeks at the dose level prior to discontinuation of therapy (see Warnings and Precautions (5.16)). Patients who reinitiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4.0 is re-established and every 12 weeks thereafter.

2.4 Dosage Modification for QT Interval Prolongation

See Table 2 for dose adjustments for QT interval prolongation (see Clinical Pharmacology (12.2)). (See Table 2) (…)

2.7 Dosage Modification for Hepatic Impairment

If possible, consider alternative therapies. If Tasigna must be administered to patients with hepatic impairment, consider the following dose reduction: (See Table 6) (…)

2.8 Dosage Modification with Concomitant Strong CYP3A4 Inhibitors

Avoid the concomitant use of strong CYP3A4 inhibitors. Should treatment with any of these agents be required, interrupt therapy with Tasigna. If patients must be coadministered a strong CYP3A4 inhibitor, reduce dosage to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP. (…)

5 WARNINGS AND PRECAUTIONS

5.12 Hemorrhage

In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Tasigna and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Tasigna 300 mg bid arm, in 1.8% patients in the Tasigna 400 mg bid arm, and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Tasigna 300 mg bid and 400 mg bid arms and in 1.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Tasigna 300 mg bid and 400 mg bid arms and in 1.4% of patients in the imatinib arm. GI hemorrhage occurred in 0.7% and 1.4% of patients in the Tasigna 300 mg bid and 400 mg bid arms, respectively, and in no patients in the imatinib arm.

5.17 Fluid Retention

In the randomized trial in patients with newly diagnosed Ph+ CML in chronic phase, severe (Grade 3 or 4) fluid retention occurred in 3.9% and 2.9% of patients receiving Tasigna 300 mg bid and 400 mg bid, respectively, and in 2.5% of patients receiving imatinib. (…)

5.14 Effects on Growth and Development in Pediatric Patients

Growth retardation has been reported in pediatric patients with Ph+ CML in chronic phase treated with Tasigna. In a pediatric trial with 58 patients with Ph+ CML in chronic phase after a median follow-up of 33 months, 12% (n = 7) of patients experienced a decrease of two main height percentile lines (percentile lines: 5th, 10th, 25th, 50th, 75th, 90th, and 95th). Adverse reactions associated with growth retardation were reported in 3 patients (5%). Monitor growth and development in pediatric patients receiving Tasigna treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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<td>In Adult Patients with Newly Diagnosed Ph+ CML-CP</td>
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<td>The data below reflect exposure to Tasigna from a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the Tasigna 300 mg twice daily group was 61 months (range 0.1 to 71 months). The median actual dose intensity was 593 mg/day in the Tasigna 300 mg twice daily group. (…) (…)</td>
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<td>In Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP</td>
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<td>In the single open-label multicenter clinical trial, a total of 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP=321; CML-AP=137) at the recommended dose of 400 mg twice daily. (…) (most frequently reported adverse reactions)</td>
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<td>Tables 7 and 8 show the percentage of adult patients experiencing non-hematologic adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in greater than 10% of adult patients who received at least 1 dose of Tasigna are listed. (See Tables 7 and 8) (…)</td>
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<td>Laboratory Abnormalities</td>
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<td>Table 9 shows the percentage of adult patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna. (See Table 9) (…)</td>
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<td>Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)</td>
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<td>The rate of musculoskeletal symptoms decreased in patients who entered the Tasigna treatment reinitiation (NTRI) phase, at 11/88 (12.5%) in the newly diagnosed population and 14/59 (25%) in the population previously treated with imatinib. Other adverse reactions observed in the Tasigna re-treatment phase were similar to those observed in patients use in patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP. (See Table 10) (…)</td>
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<td>Additional Data from Clinical Trials</td>
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<td>The following adverse drug reactions were reported in adult patients in the Tasigna clinical studies at the recommended doses. These adverse drug reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (greater than or equal to 1% and less than 10%), uncommon (greater than or equal to 0.1% and less than 1%), and unknown frequency (single events). For laboratory abnormalities, very common events (greater than or equal to 10%), which were not included in Tables 7 and 8, are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category, obtained from 2 clinical studies:</td>
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<td>1. Adult patients with newly diagnosed Ph+ CML-CP 60 month analysis and,</td>
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<td>2. Adult patients with resistant or intolerant Ph+ CML-CP and CML-AP 24 months’ analysis (…) (…)</td>
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<td>In Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP</td>
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<td>The data below reflect exposure to Tasigna from two studies in pediatric patients from 2 to less than 18 years of age with either newly diagnosed Ph+ CML-CP or CML-AP resistant or intolerant Ph+ CML-CP treated at the recommended dose of 230 mg/m2 twice daily (n=69) [see Clinical Studies (14.5)]. The median time on treatment with Tasigna was 13.8 months (range: 0.7 to 30.9 months). The median actual dose intensity was 435.5 mg/m2/day (range: 149 to 517 mg/m2/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 100%. In pediatric patients with Ph+ CML-CP, the most common (greater than 20%) non-hematologic adverse drug reactions were headache, rash, hyperbilirubinemia, alanine aminotransferase increased, pyrexia, nausea, upper respiratory tract infection, aspartate aminotransferase increased, and vomiting. The most common (greater than or equal to 5%) Grade 3/4 non-hematologic adverse drug reactions were alanine aminotransferase increased and hyperbilirubinemia. (…) Growth Retardation in Pediatric Population</td>
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<td>In a multicenter, open-label, single-arm study of 58 pediatric patients with newly diagnosed or resistant Ph+ CML-COP treated with Tasigna, with a median exposure of 33 months in each cohort, adverse reactions associated with growth and deceleration of growth in regard to height were reported in 3 patients (5%). The adverse reactions include growth retardation in 2 adolescent patients and growth hormone deficiency with body height below normal in the remaining patient (age category: child). Of the 58 pediatric patients, 12% (n = 7) experienced a decrease of two main height percentiles compared with baseline (percentile lines: 5th, 10th, 25th, 50th, 75th, 90th, and 95th). Close monitoring of growth in pediatric patients under Tasigna treatment is recommended [see Warnings and Precautions (5.14)].</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.4 Pediatric Use</td>
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<td>The safety and effectiveness of Tasigna have been established in pediatric patients greater than or equal to 1 year of age with newly diagnosed and resistant or intolerant Ph+ CML in chronic phase [see Clinical Studies (14.5)]. There are no data for pediatric patients under 2 years of age. Use of Tasigna in pediatric patients 1 to less than 2 years of age is supported by efficacy in pediatric patients 2 to 6 years of age. Use of Tasigna in pediatric patients 1 to less than 18 years of age is supported by evidence from two clinical trials [see Clinical Studies (14.5)]. The 25 patients with newly diagnosed Ph+ CML-CP were in the following age groups: 6 children (age 2 to less than 12 years) and 19 adolescents (age 12 to less than 18 years). The 44 patients with resistant or intolerant Ph+ CML-CP included 18 children (age 2 to less than 12 years) and 26 adolescents (age 12 to less than 18 years). (…)</td>
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<td>8.5 Geriatric Use</td>
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<td>In the clinical trials of Tasigna (patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP), approximately 12% and 30% of patients were 65 years or over respectively.</td>
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<td>• Patients with newly diagnosed Ph+ CML-CP: There was no difference in major molecular response between patients aged less than 65 years and those greater than or equal to 65 years. (…)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once or twice daily dosing. In adult patients with resistant or intolerant Ph+ CML given Tasigna 400 mg twice daily, the steady-state mean (CV%) Cmax and AUC0-12h were 2260 ng/ml (35%) and 18000 ng∙h/ml (33%), respectively. In adult patients with newly diagnosed Ph+ CML given Tasigna 300 mg twice daily, the steady-state mean (CV%) Cmax and AUC0-12h were 1540 ng/ml (48%) and 13337 ng∙h/ml (46%), respectively. (…) 12.3 Pharmacokinetics

Specific Populations

Age, sex, race/ethnicity, or body weight did not significantly affect the pharmacokinetics of nilotinib. The effect of renal impairment on nilotinib pharmacokinetics is unknown.

Pediatric Patients

Following administration of the approved pediatric dosage of nilotinib, steady-state exposure of nilotinib were within 2-fold to adult patients treated with 400 mg twice daily. Steady-state Cmin was comparable across all age groups (pediatric patients from ages 2 to less than 18 years), diseases (patients with newly diagnosed and resistant or intolerant Ph+ CML) and studies.

Body surface area correlated with nilotinib clearance and was the primary factor responsible for the PK differences between pediatrics and adults.

14 CLINICAL STUDIES

14.1 Adult Newly Diagnosed Ph+ CML-CP

The ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Newly Diagnosed patients) study (NCT00471497) was an open-label, multicenter, randomized trial conducted to determine the efficacy of Tasigna versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. Efficacy was based on a total of 846 patients: 283 patients in the imatinib 400 mg once daily group, 282 patients in the Tasigna 300 mg twice daily group, 281 patients in the Tasigna 400 mg twice daily group. (…)

The primary efficacy endpoint was major molecular response (MMR) at 12 months after the start of study medication. MMR was defined as less than or equal to 0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a greater than or equal to 3 log reduction of BCR-ABL transcript from standardized baseline. Efficacy endpoints are summarized in Table 12. (See Table 12) (…) 14.2 Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP

Study CAMIN017A2101 (referred to as Study A2101) (NCT00190707) was a single-arm, open-label, multicenter study conducted to evaluate the efficacy and safety of Tasigna (400 mg twice daily) in patients with imatinib-resistant or intolerant CML with separate cohorts for chronic and accelerated phase disease. The definition of imatinib resistance included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance was defined as discontinuation due to toxicity and lack of a major cytogenetic response at time of study entry. At the time of data cutoff, 321 patients with CML-CP and 137 patients with CML-AP with a minimum follow-up of 24 months were enrolled. In this study, about 50% of CML-CP and CML-AP patients were males, over 90% (CML-CP) and 80% (CML-AP) were Caucasian, and approximately 30% were age 65 years or older. 14.3 Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)

The ENESTfreedom (Evaluating Nilotinib Efficacy and Safety in clinical Trials-freedom) study (NCT01784068) is an open-label, multicenter, single-arm study, where 215 adult patients with Ph+ CML-CP treated with Tasigna in first-line for ≥ 2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 190 patients (88.4%) entered the “Treatment-free Remission” (TFR) phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

- The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS)
- No more than two assessments falling between MR4 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤ 0.01% IS)
- The median age of patients who entered the TFR phase was 55 years, 49.5% were females, and 21.1% of the patients were ≥ 65 years of age. BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:
  - Loss of MMR requiring patient to reinitiate Tasigna treatment
  - When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
  - When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).
  - No more than two assessments falling between MR4 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤ 0.01% IS) during 1 year.

14.4 Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5) on Tasigna following prior imatinib therapy

The ENESTTop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-StTop) study (NCT01698905) is an open-label, multicenter, single-arm study, where 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥ 3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to Tasigna, then switched to Tasigna for at least 2 years), and who achieved MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 120 patients (77.3%) entered the TFR phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

- The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during 1 year.
- Loss of MMR requiring patient to reinitiate Tasigna treatment
  - When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
  - When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

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**14.5 Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP**

The safety and efficacy of Tasigna in pediatric patients with Ph+ CML-CP have been investigated in two studies: Study CAMN107A2120 (NCT01077544), an open-label, single-arm, multi-center study that evaluated the pharmacokinetics, safety, and preliminary efficacy of Tasigna in pediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib (n=11), and Study CAMN107A2203 (NCT01844765), an open-label, single-arm, multi-center study evaluating the efficacy and safety of Tasigna in pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib (n=33) and newly diagnosed Ph+ CML-CP (n=48). In both studies, patients received Tasigna treatment at a dose of 250 mg/m² twice daily, rounded to the nearest single dose of 400 mg. Data was pooled from a total of 69 pediatric patients (from 2 to less than 18 years of age) with either newly diagnosed Ph+ CML-CP (n=25; 6 children from 2 to less than 12 years and 19 adolescents from 12 to less than 18 years) or imatinib/dasatinib resistant or intolerant Ph+ CML-CP (n=44; 18 children from 2 to less than 12 years and 26 adolescents from 12 to less than 18 years).

The median time on treatment with Tasigna was 13.80 months (range: 0.7 to 30.9 months).

In patients with resistant or intolerant CML, the major molecular response (MMR) rate among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment was 47.7% (21/44) by cycle 12. In patients with newly diagnosed CML, the cumulative MMR rate was 60.0% (15/25; 95% CI: 38.3%, 78.9%) at 12 cycles (28 days per cycle). In patients with newly diagnosed CML, the MMR rate was 60.0% (15/25; 95% CI: 38.3%, 78.9%) at 12 cycles. In patients with resistant or intolerant CML, the cumulative MMR rate was 47.7% (21/44) by cycle 12. In patients with newly diagnosed CML, the cumulative MMR rate was 64.0% (16/25) by cycle 12.

Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, the median time to first MMR was 2.8 months (range: 0.0 to 64.0% (16/25) by cycle 12.

Among patients with newly diagnosed CML, the percentage of patients who achieved MR4.5 was 28.0% (See Table 13) (…)

**2.2 Recommended Dosage**

The recommended dosage of ZEJULA is 300 mg (three 100-mg capsules) taken orally once daily. For the maintenance treatment of recurrent ovarian cancer, patients should start treatment with ZEJULA no later than 8 weeks after their most recent platinum-containing regimen.

**6 ADVERSE REACTIONS**

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 136 patients with platinum-sensitive recurrent gBRCAmut ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Table 8 and Table 9 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in the gBRCAmut cohort of the NOVA trial. The following adverse reactions have been identified in ≥1 to <10% of the 136 patients receiving ZEJULA in the gBRCAmut cohort of the NOVA trial and not included in the table: palpitations (9%), mucositis/stomatitis (9%), MDS/AML (7%), tachycardia (7%), and bronchitis (4%).

**14 CLINICAL STUDIES**

**14.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer**

(…) Patients were randomized post completion of first-line platinum-based chemotherapy plus surgery. Randomization was stratified by best response during the front-line platinum regime (complete response vs partial response), neoadjuvant chemotherapy (NACT) (yes vs no), and HRD status (positive vs negative or not determined). HRD status was determined using the FDA-approved Myriad myChoice CDx assay. HRD positive status included either tumor BRACA mutant (tBRCAm) or a genomic instability score (GIS) ≥ 42.

The major efficacy outcome measure, progression-free survival (PFS), was determined by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In some cases, criteria other than RECIST, such as clinical signs and symptoms and increasing CA-125, were used.

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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.

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<td>11/27/2023</td>
<td>Nirogacestat (1)</td>
<td>Oncology</td>
<td>APC</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Desmoid Tumor (…) A total of 142 patients were randomized. The median age was 34 years (range: 18 to 76); 65% were female; race was 83% White, 6% Black, 3% Asian, and other or not reported in 8%; and 73% had an ECOG performance status (PS) of 0, 27% had an ECOG PS of 1, and 0% had an ECOG PS of 2. Twenty-three percent of patients had intra-abdominal disease or both intraand extra-abdominal disease, and 77% had only extra-abdominal disease. Forty-one percent of patients had multifocal disease and 59% had single focal disease. Of 105 patients with known tumor mutation status, 81% had a CTNNB1 mutation and 21% had an APC mutation. Seventeen percent of patients had a family history of familial adenomatous polyposis (FAP). (…)</td>
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<td>Clinical Studies</td>
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<td>11/04/2013</td>
<td>Nitrofurantoin</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>WARNINGS Hemolytic anemia Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphatedehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn. ADVERSE REACTIONS Laboratory Adverse Events The following laboratory adverse events have been reported with the use of nitrofurantoin; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see Warnings), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.</td>
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| 125554, 10/13/2023                     | Nivolumab (1) | Oncology | BRAF | Adverse Reactions, Clinical Studies | 6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Unresectable or Metastatic Melanoma
Previously Treated Metastatic Melanoma
(...)
...In CHECKMATE-037, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (...)
...Previously Untreated Metastatic Melanoma
CHECKMATE-066
The safety of OPDIVO was also evaluated in Trial 4, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m² every 3 weeks (n=205) [see Clinical Studies (14.1)]. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. (...)

| 125554, 10/13/2023                     | Nivolumab (2) | Oncology | CD274 (PD-L1) | Indications and Usage, Dosage and Administration, Use in Specific Populations, Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
1.4 Metastatic Non-Small Cell Lung Cancer
• OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations.

| 125554, 10/13/2023                     | Nivolumab (2) | Oncology | CD274 (PD-L1) | Indications and Usage, Dosage and Administration, Use in Specific Populations, Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
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14 CLINICAL STUDIES
14.1 Unresectable or Metastatic Melanoma
Previously Untreated Metastatic Melanoma
CHECKMATE-066
(…) Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). (…) Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (44%). Reference ID: 4198384 (11%), elevated LDH level (37%), PD-L1 greater than or equal to 5% tumor cell membrane expression (35%), and history of brain metastasis (4%). (…) CHECKMATE-067
(…) Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). (…) The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 67% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (68%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%). (…) 14.2 Adjuvant Treatment of Melanoma
CHECKMATE-238
(…) Randomization was stratified by PD-L1 status (positive [based on ≥1% level] vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage III/C vs Stage IV M1a-M1b vs Stage IV M1c). (…) Disease characteristics were AJCC Stage IIIb (34%), Stage IIIc (47%), Stage IV (19%), M1a (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%). (…) 14.3 Metastatic Non-Small Cell Lung Cancer (NSCLC)
First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Ipilimumab
CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer (IASLC) classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. (…) Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDX assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). (…) In Part 1a, a total of 793 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers. The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the OPDIVO and ipilimumab arm compared with the platinum-doublet chemotherapy arm. The OS results are presented in Table 35 and Figure S. (…) First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Iplimumab and Platinum-Doubl elet Chemotherapy
CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment. (…) Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m2, or cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 for non-squamous, or carboplatin (AUC 6) and paclitaxel 200 mg/m2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or nonquantifiable), histology (squamous versus non-squamous), and sex (male versus female). (…) A total of 719 patients were randomized to receive either OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (85%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers. (…) Second-line Treatment of Metastatic Squamous NSCLC
CHECKMATE-017
(…) This study included patients regardless of their PD-L1 status. (…) Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the study population, 17% (47/272) of patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% (106/225) had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1, and 53% (119/225) had PD-L1 positive squamous NSCLC, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive NSCLC subgroup. (…) Second-line Treatment of Metastatic Non-Squamous NSCLC

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<td><strong>CHECKMATE-057</strong></td>
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<td>(…) The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression. (…) Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (208/455) PD-L1 negative, defined as &lt;1% of tumor cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% (65/246) had ≥1%, but &lt;5% tumor cells with positive staining, 7% (16/246) had ≥5% but &lt;10% tumor cells with positive staining, and 67% (165/246) had greater than or equal to 10% tumor cells with positive staining. Prespecified analyses of survival results determined by percentage of tumor cells expressing PD-L1. Figure 10 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1. (See Figures 9 and 10) (…)</td>
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<td><strong>CHECKMATE-032 (NCT01928394)</strong></td>
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<td>14.5 Advanced Renal Cell Carcinoma Previously Treated Renal Cell Carcinoma CHECKMATE-025 (NCT01688784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior antiangiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. (…) (…) OS benefit was observed regardless of PD-L1 expression level. (See Table 40) (…)</td>
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<td>Previously Untreated Renal Cell Carcinoma CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. (…) (…) OS benefit was observed regardless of PD-L1 expression level. (See Table 41) (…)</td>
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<td>Two studies evaluated the efficacy of OPDIVO as a single agent in patients with cHL after failure of autologous HSCT.</td>
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<td><strong>CHECKMATE-205 (NCT02181738)</strong></td>
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<td>14.6 Classical Hodgkin Lymphoma CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort study in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation study that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. (…) Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT. CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance &lt;40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity. (…)</td>
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<td><strong>CHECKMATE-141</strong></td>
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<td>14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (US/Canada/Western Europe/Northern Europe vs. Rest of World). (…) Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the study population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as &lt;1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified analyses of survival results determined by percentage of tumor cells expressing PD-L1. Figure 10 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1. (See Figures 9 and 10) (…)</td>
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<td>125554, 10/13/2023</td>
<td>Nivolumab (3)</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.9 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer Nivolumab, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.9)]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
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<td>2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosage The recommended dosages of OPDIVO as a single agent are presented in Table 1. [See Tables 1 and 2].</td>
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<td>6 ADVERSE REACTIONS MSI-H or dMMR Metastatic Colorectal Cancer The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label study. [See Tables 20 and 27].</td>
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<td>8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use</td>
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<td>Nivolumab (4)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>The safety and effectiveness of OPDIVO have been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater for this indication is the same as that in adults [see Dosage and Administration (2.8), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]. The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients less than 18 years old for the other approved indications.</td>
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14 CLINICAL STUDIES

14.9 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

CHECKMATE-142 (NCT02050188) was a multicenter, open-label, single-arm study conducted in patients with locally determined MSI-H or dMMR metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. (…) Patients enrolled in the single-agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg IV every 4 weeks for 4 doses, followed by OPDIVO 3 mg/kg IV as a single agent every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (…) A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% <70 years of age, 59% were male and 88% were White. (…) A total of 119 patients were enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort. (See Table 56) (…)

14.3 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-arm study conducted in patients with locally determined MSI-H or dMMR metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. (…) A total of 74 patients were enrolled in the single-agent MSI-H mCRC cohort. (See Table 56) (…)

6 ADVERSE REACTIONS

Metastatic Non-Small Cell Lung Cancer

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations. (See Table 54) (…)

14 CLINICAL STUDIES

14.3 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1), with no EGFR or ALK genomic tumor aberrations. (…) Patients enrolled in the single-agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg IV every 4 weeks for 4 doses, followed by OPDIVO 3 mg/kg IV as a single agent every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (…) A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% <70 years of age, 59% were male and 88% were White. (…) A total of 119 patients were enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort. (See Table 56) (…)

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| 125554, 10/13/2023                     | Nivolumab (5) | Oncology         | ALK        | Indications and Usage, Adverse Reactions, Clinical Studies | **1 INDICATIONS AND USAGE**

**1.4 Metastatic Non-Small Cell Lung Cancer**

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 ≥1% as determined by an FDA-approved test [see Dosage and Administration (2.1), with no EGFR or ALK genomic tumor aberrations.
- OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- OPDIVO is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

**6 ADVERSE REACTIONS**

Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.3)].

**14 CLINICAL STUDIES**

**14.3 Metastatic Non-Small Cell Lung Cancer**

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Ipilimumab

The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. (…) First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [ASLC]). ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment. (…) Second-line Treatment of Metastatic Non-Squamous NSCLC

(…) CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. (…) The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (65%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. (…)  **6 ADVERSE REACTIONS**

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

The safety of OPDIVO in combination with chemotherapy was evaluated in CHECKMATE649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma [see Clinical Studies (14.12)].

The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

**14 CLINICAL STUDIES**

**14.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma**

CHECKMATE-649 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases.

**14 CLINICAL STUDIES**

**14.1 Clinical Studies**

**14.1.1 Nivolumab and Relatlimab-mbwy (1)**

Nivolumab and Relatlimab-mbw (1)

Oncology         | BRAF (1) | Clinical Studies |

The efficacy of OPDUALAG was investigated in RELATIVITY-047 (NCT03470922), a randomized (1:1), double-blinded trial in 714 patients with previously untreated metastatic or unresectable Stage III or IV melanoma. (…) Randomization was stratified by tumor PD-L1 expression (≥1% vs. <1%) using a clinical trial assay, BRAF V600 mutation status (V600 mutation positive vs. wild-type), and M stage per the American Joint Committee on Cancer (AJCC) version 8 staging system (M0/M1any [0] vs. M1any [1]). The trial population characteristics were: median age 63 years (range: 20 to 94); 58% male; 97% White 0.7% African American, and American Indian/Alaskan Native 0.1%; Hispanic 7%; and ECOG performance score was 0 (67%) or 1 (33%). Disease characteristics were: PD-L1 expression ≥1% (41%), LAG-

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| 018013, 04/09/2019 | Nortriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS: 
Drugs Metabolized by P450 2D6 |
The biochemical activity of the drug metabolizing isocitrate cytochrome P450 2D6 (debrisosquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isoenzyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCA)s when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (6 fold increase in plasma AUC of the TCA). |
| 209531, 10/10/2018 | Nusinersen | Neurology | SMN2 | 12 CLINICAL PHARMACOLOGY: 
12.2 Pharmacodynamics |
Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants. |
| 125486, 03/27/2020 | Obinutuzumab | Oncology | MS4A1 (CD20 antigen) | Clinical Studies | 14 CLINICAL STUDIES: 
14.1 Chronic Lymphocytic Leukemia |
GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (Study 1) in 781 patients with previously untreated metastatic or unresectable Stage III or IV melanoma. (…) Baseline demographics were balanced between the GAZYVA and control groups with the exception of age at first treatment (median age 63 years (range: 20 to 94); 58% male; 97% White 0.7% African American, and American Indian/Alaskan Native 0.1%; Hispanic 7%; and ECOG performance score was 0 (67%) or 1 (33%). Disease characteristics were: PD-L1 expression ≥1% (41%), LAG-3 expression (≥1% vs. <1%) using a clinical trial assay, BRAF V600 mutation status (V600 mutation positive vs. wild type), and M stage per the American Joint Committee on Cancer (AJCC) version 8 staging system (M0/M1any [0] vs. M1any [1]). |
| 215498, 06/13/2023 | Odevixibat (1) | Gastroenterology | ABCB11 | Indications and Usage, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE |
BLYVAY is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC). |
Limitations of Use: 
- BLYVAY may not be effective in PFIC type 2 patients with ABCB11 variants resulting in nonfunctional or complete absence of bile salt export pump protein (BSEP-3). |
| 761234, 03/18/2022 | Nivolumab and Relatlimab-rmbw (2) | Oncology | CD274 (PD-L1) | Clinical Studies | 14 CLINICAL STUDIES: 
14.3 Presymptomatic SMA |
(…) Baseline demographics were balanced between the SPINRAZA and control groups with the exception of age at first treatment (median age 63 years (range: 20 to 94); 58% male; 97% White 0.7% African American, and American Indian/Alaskan Native 0.1%; Hispanic 7%; and ECOG performance score was 0 (67%) or 1 (33%). Disease characteristics were: PD-L1 expression ≥1% (41%), LAG-3 expression (≥1% vs. <1%) using a clinical trial assay, BRAF V600 mutation status (V600 mutation positive vs. wild type), and M stage per the American Joint Committee on Cancer (AJCC) version 8 staging system (M0/M1any [0] vs. M1any [1]). |

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<td>215498, 06/13/2023</td>
<td>Odevixibat (2)</td>
<td>Gastroenterology</td>
<td>ATP8B1</td>
<td>Indications and Usage, Clinical Pharmacology, Clinical Studies</td>
<td>BYLVAY is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC). Clinical Limitations: BYLVAY may not be effective in PFIC type 2 patients with ABCB11 variants resulting in nonfunctional or complete absence of bile salt export pump protein (BSEP-3).</td>
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<tr>
<td>215498, 06/13/2023</td>
<td>Odevixibat (3)</td>
<td>Gastroenterology</td>
<td>JAG1</td>
<td>Clinical Studies</td>
<td>BYLVAY is efficacious in pediatric patients, aged 6 months to 17 years, with confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.</td>
</tr>
<tr>
<td>215498, 06/13/2023</td>
<td>Odevixibat (4)</td>
<td>Gastroenterology</td>
<td>NOTCH2</td>
<td>Clinical Studies</td>
<td>BYLVAY is efficacious in pediatric patients, aged 6 months to 17 years, with confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.</td>
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14 CLINICAL STUDIES

The efficacy of BYLVAY was evaluated in Trial 1 (NCT03566238), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 1 was conducted in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.

The efficacy of BYLVAY was evaluated in Trial 2 (NCT04674761), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 2 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 2.

The efficacy of BYLVAY was evaluated in Trial 3 (NCT03566238), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 3 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 3.

The efficacy of BYLVAY was evaluated in Trial 3 (NCT03566238), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 3 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 3.

14 CLINICAL STUDIES

The efficacy of BYLVAY was evaluated in Trial 1 (NCT03566238), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 1 was conducted in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.

The efficacy of BYLVAY was evaluated in Trial 1 (NCT03566238), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 1 was conducted in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.

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The efficacy of BYLVAY was evaluated in Trial 1 (NCT03566238), a 24-week, randomized, doubleblind, placebo-controlled trial. Trial 1 was conducted in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-functional or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.
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| 208558, 05/31/2023                     | Olaparib (1)  | Oncology          | BRCA       | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer  
Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab  
Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:  
- a deleterious or suspected deleterious BRCA mutation, and/or  
- genomic instability.  
Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.3 First-line Maintenance Treatment of Germline BRCA-mutated HER2-negative High Risk Early Breast Cancer  
Lynparza is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epithelial growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.4 Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy  
Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.5 Adjuvant Treatment of Germline BRCA-mutated HER2-negative Metastatic Breast Cancer  
Lynparza is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.6 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer  
Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.7 First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma  
Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.8 Treatment of BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone  
Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
2.1 Patient Selection  
Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics. Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).  
2.2 Recommended Dosing  
First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer  
Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.  
Recurrent Ovarian Cancer, Germline BRCAm Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HER2 Gene-mutated Metastatic Castration-Resistant Prostate Cancer  
Continue treatment until disease progression or unacceptable toxicity for:  
- Maintenance treatment of recurrent ovarian cancer  
- Advanced germline BRCA-mutated ovarian cancer  
- Germline BRCA-mutated HER-2 negative metastatic breast cancer  
- First-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma. (…)  
5 WARNINGS AND PRECAUTIONS  
5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia  
In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent [see Adverse Reactions (6.1)], the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was <1.5% (28/2351) and the majority of events had a fatal outcome. Of these, 25/28 patients had a documented BRCA mutation, 2 patients had gBRCA wildtype and in 1 patient the BRCA mutation status was unknown. (…)  

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Blue text represents the most recent additions and/or changes since last posted version.
14.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer

The efficacy of Lynparza was evaluated in SOLO-1 (NCT01844986), a randomized (2:1), double-blind, placebo-controlled, multi-center trial in patients with BRCA-mutated advanced ovarian cancer following first-line platinum-based chemotherapy. The majority of patients were randomized to receive either Lynparza tablets 300 mg orally twice daily or placebo tablets twice daily. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year. (…)

Treatment of BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

The safety of Lynparza for the maintenance treatment of patients with BRCA-mutated advanced ovarian cancer following first-line platinum-based chemotherapy was evaluated in PROpel (NCT02477644) as a randomized, open-label, multi-center study in which 386 patients were randomized to receive either Lynparza tablets 300 mg orally twice daily or investigator’s choice of enzalutamide or abiraterone in PROfound (see Clinical Studies (14.8)). Patients were randomized to receive either Lynparza tablets 300 mg orally twice daily or placebo tablets 1000 mg once daily (Lynparza/abiraterone) (n=398), or placebo plus abiraterone 1000 mg once daily (placebo/abiraterone) (n=398) until disease progression or unacceptable toxicity. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily. (…)

14.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1

PAOLA-1 (NCT02477644) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomization was stratified by first-line treatment outcome (limping and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and iBRCAn status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx. (…)

14.3 Maintenance Treatment of Recurrent Ovarian Cancer

The efficacy of Lynparza was investigated in two randomized, placebo-controlled, double-blind, multicenter studies in patients with recurrent ovarian cancers who were in response to platinum-based therapy.
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SOLO-2
The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874353), a randomized (2:1) double-blind, placebo-controlled trial in patients with gBRCAm ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomized to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. (…)

All patients had a deleterious or suspected deleterious germline BRCA mutation as detected either by a local test (n=236) or central Myriad CLIA test (n=59), subsequently confirmed by BRACAnalysis CDx® (n=206). (…)

Study 19
A retrospective analysis for germline BRCA mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious gBRCA mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo. (…)

14.4 Advanced Germline BRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy
The efficacy of Lynparza was investigated in a single-arm study of patients with deleterious or suspected deleterious gBRCAm advanced cancers. A total of 137 patients with measurable, advanced gBRCAm ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules 400 mg orally twice daily until disease progression or intolerable toxicity. The efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by the investigator according to RECIST, version 1.0. (…)

14.5 Adjuvant Treatment of Germline BRCA-mutated HER2-negative High Risk Early Breast Cancer
The efficacy of Lynparza was evaluated in OlympiA (NCT02032823), a randomized (1:1), double-blind, placebo-controlled, international study in patients with gBRCAm HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. (See Table 25)

- patients who received prior adjuvant chemotherapy; patients with TNBC must have had node positive disease or node negative disease with a 2cm primary tumor; patients with hormone receptor positive, HER2-negative breast cancer must have had ≥4 pathologically confirmed positive lymph nodes. (…)

Patients enrolled based on local gBRCA test results provided a sample for retrospective confirmatory central testing with BRACAnalysis®. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as gBRCAm by Myriad BRACAnalysis®, either prospectively or retrospectively. (…)

14.6 Treatment of Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomized (2:1) study in patients with gBRCAm HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. (…)

Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious gBRCAm status. 202 were randomized to the Lynparza arm and 95 to the healthcare provider’s choice of chemotherapy arm. (…)

14.7 Treatment of Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomized (2:1) study in patients with gBRCAm HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. (…)

Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious gBRCAm status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider’s choice of chemotherapy arm. (…)

14.7 First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma
The efficacy of Lynparza was evaluated in POLO (NCT02184196), a randomized (3:2), double-blind placebo-controlled, multi-center trial. Patients were required to have metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline BRCA mutation (gBRCAm) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. (…)

All patients had a deleterious or suspected deleterious germline BRCA mutation as detected by the Myriad BRACAnalysis® or BRACAnalysis CDx® at a central laboratory only (n=100), local BRCA test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in BRCA1; 69% had a mutation in BRCA2; and 1 patient (1%) had mutations in both BRCA1 and BRCA2. Efficacy results of POLO are provided in Table 24 and Figure 6. (…)

14.8 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer
(…)

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized in Cohort B; patients with comutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort B. (…)

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine FDx® tissue-based assay and assessment of the germline-BRCA status using the Myriad BRACAnalysis CDx® blood-based assay was performed retrospectively. Representation of individual gene mutations by cohort is provided in Table 25. (…)

No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: FANCL and RAD51C. (See Table 25)

14.9 Treatment of BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone
The efficacy of Lynparza in the treatment of patients with mCRPC was investigated in PROpel (NCT03732820), a randomized, double-blind, placebo-controlled, multi-center study that compared the efficacy of Lynparza in combination with abiraterone plus placebo with abiraterone for patients with mCRPC. (…)

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<td>Olaparib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>BRCA gene mutation (BRCAm) status was assessed after randomization and before primary analysis by both NGS-based tumor tissue and ctDNA tests. BRCAm classification criteria in line with the FDA approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status of patients. (...) Of the 796 patients tested, 85 (11%) had BRCAm determined by either a positive ctDNA test (9%) or a tumor tissue test (6%). Among these 85 patients, the median age was 66 years (range 43 to 85), and 67% were 65 years or older; 72% were White, 22% Asian, and 2% Black or African American; 66% had ECOG performance status (PS) 0 and 34% had ECOG PS 1; 25% had prior docetaxel treatment for mHSPC; 53% had bone-only metastases, 19% had visceral metastases, and 32% had other metastases. A statistically significant improvement in rPFS for Lynparza/abiraterone compared to placebo/abiraterone was observed in the intention to treat (ITT) population. In an exploratory analysis in the subgroup of 711 patients without an identified BRCAm, the rPFS hazard ratio was 0.77 (95% CI: 0.63, 0.96) and the OS hazard ratio was 0.92 (95% CI: 0.74, 1.14), indicating that the improvement in the ITT population was primarily attributed to the results seen in the subgroup of patients with BRCAm. Results of an exploratory analysis in the subgroup of 85 patients on PROpel with BRCAm are summarized in Table 31 and Figure 12. Results from the BICR assessment were consistent with the investigator-assessed rPFS results.</td>
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| **208558, 05/31/2023**                 | Olaparib (3) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Clinical Studies | **1 INDICATIONS AND USAGE**

**1.5 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer**

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].

**14 CLINICAL STUDIES**

**14.4 Adjuvant Treatment of Germline BRCA-mutated HER2-negative High Risk Early Breast Cancer**

The efficacy of Lynparza was evaluated in OlympiA (NCT02032823), a randomized (1:1), double-blind, placebo-controlled, international study in patients with gBRCAm HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. (See Table 25)

- patients who received prior adjuvant chemotherapy: patients with TNBC must have had node positive disease or node negative disease with a ≥2 cm primary tumor; patients with hormone receptor positive, HER2-negative breast cancer must have had ≥4 pathologically confirmed positive lymph nodes. (…)

Patients enrolled based on local gBRCA test results provided a sample for retrospective confirmatory central testing with BRACAnalysis®. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as gBRCAm by Myriad BRACAnalysis®, either prospectively or retrospectively. (…)

**14.6 Treatment of Germline BRCA-mutated HER2-negative Metastatic Breast Cancer**

The efficacy of Lynparza was evaluated in OlympiA (NCT02032823), an open-label randomized (2:1) study in patients with gBRCAm HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have had hormone receptor positive disease with a ≥2 cm primary tumor; patients with hormone receptor positive, HER2-negative breast cancer must have had ≥4 pathologically confirmed positive lymph nodes. (…)

Patients enrolled based on local gBRCA test results provided a sample for retrospective confirmatory central testing with BRACAnalysis®. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as gBRCAm by Myriad BRACAnalysis®, either prospectively or retrospectively. (…)

| **208558, 05/31/2023** | Olaparib (4) | Oncology | BRCA, Genomic Instability (Homologous Recombination Deficiency) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | **1 INDICATIONS AND USAGE**

**1.2 First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab**

Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious BRCA mutation, and/or
- genomic instability.

Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

**2.2 Recommended Dosage**

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare professional, should continue treatment to delay symptoms.

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| 208558, 05/31/2023                     | Olaparib | Oncology        | Homologous Recombination Repair | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  

1.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer  

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious HRR gene mutations, including BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).  

2 DOSAGE AND ADMINISTRATION  

2.1 Patient Selection  

Information on FDA-approved tests for the detection of genetic mutations is available at [http://www.fda.gov/companionsidiagnostics](http://www.fda.gov/companionsidiagnostics).  

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).  

2.2 Recommended Dosage  

Recurrent Ovarian Cancer, Germline BRCA-mutated Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer  

Continue treatment until disease progression or unacceptable toxicity for:  

- Maintenance treatment of recurrent ovarian cancer  
- Advanced germline BRCA-mutated ovarian cancer  
- Germline BRCA-mutated HER-2 negative metastatic breast cancer  
- First-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma.  
- HRR gene-mutated metastatic castration-resistant prostate cancer.  

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchectomy.

6 ADVERSE REACTIONS  

6.1 Clinical Trial Experience  

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab  

PAOLA-1  

The safety of Lynparza in combination with bevacizumab for the maintenance treatment of patients with advanced ovarian cancer following first-line treatment containing platinum-based chemotherapy and bevacizumab was investigated in PAOLA-1 [see Clinical Studies (14.2)].  

14 CLINICAL STUDIES  

14.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab  

PAOLA-1  

PAOLA-1 (NCT02477644) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomization was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and BRCAm status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx.  

(…) Demographics and baseline disease characteristics were balanced and comparable between the study and placebo arms in the Intention to Treat (ITT) population and also in the HRD-positive subgroup. Efficacy results from a biomarker subgroup analysis of 387 patients with HRD-positive tumors, identified post-randomization using the Myriad myChoice® HRD Plus tumor test, who received Lynparza/bevacizumab (n=265) or placebo/bevacizumab (n=132), are summarized in Table 19 and Figure 2. Results from a blinded independent review of PFS were consistent. Overall survival data in this subpopulation were immature with 16% deaths. (See Table 19 and Figure 2)  

1 INDICATIONS AND USAGE  

1.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer  

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.  

Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].

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#### HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

The efficacy of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound (see Clinical Studies (14.7)).

### 14 CLINICAL STUDIES

#### 14.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), a randomized, open-label, multicenter trial that evaluated the efficacy of Lynparza 300 mg twice daily versus a comparator arm of investigator’s choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (mCRPC). All patients received a GnRH analog or had prior bilateral orchiectomy. Patients needed to have progressed on prior enzalutamide or abiraterone for the treatment of metastatic prostate cancer and/or CRPC and have a tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized to Cohort A; patients with mutations among 12 other genes involved in the HR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized to Cohort B; patients with comutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A. Although patients with PPP2R2A gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit.

Patients with HRR gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory.

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine FoundationOne® assay. Patients with meaningful HRR mutation status were included in the analysis. The safety and efficacy of Lynparza were compared with investigator’s choice of abiraterone or enzalutamide.

Response data by HRR mutations for patients in the Lynparza Arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an ATM mutation alone and 2 patients with co-occurring mutations (one with PALB2+PPP2R2A and one with CDK12+PALB2).

#### 14.7.1 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Response data by HRR mutations for patients in the Lynparza Arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an ATM mutation alone and 2 patients with co-occurring mutations (one with PALB2 and one with CDK12+PALB2).

#### 14.7.2 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Response data by HRR mutations for patients in the Lynparza Arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an ATM mutation alone and 2 patients with co-occurring mutations (one with PALB2 and one with CDK12+PALB2).

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| 215814, 12/01/2022 | Olutasidenib | Oncology | IDH1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | REZLIDHIA was given orally at a dose of 150 mg twice daily until disease progression, development of unacceptable toxicity, or hematopoietic stem cell transplantation. Sixteen of the 147 patients (11%) underwent stem cell transplantation following R1 INDICATIONS AND USAGE.

8 USE IN SPECIFIC POPULATIONS
8.8 Poor Metabolizers of CYP2D6 Substrates
In patients who are known or suspected to be poor CYP2D6 metabolizers, based on genotype or previous history/experience with other CYP2D6 substrates, less frequent dosing of OLINVYK may be required. These patients should be closely monitored, and subsequent doses should be based on the patient’s severity of pain and response to treatment. (…)

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Drug Interactions
In vitro studies suggest that oliceridine is metabolized primarily by the CYP3A4 and CYP2D6 P450 hepatic enzymes, with minor contributions from CYP2C9 and CYP2C19. Inhibition studies using selective inhibitors of all the major CYP enzymes show that only the inhibition of CYP3A4 and CYP2D6 significantly affects the metabolism of oliceridine in these assays, suggesting that the contribution of CYP2C9 and CYP2C19 to the metabolism of oliceridine is minor. The effect of concomitant administration of a CYP2D6 inhibitor on the pharmacokinetics of OLINVYK, although not studied, may be similar to that noted in subjects who are CYP2D6 poor metabolizers. The plasma clearance of oliceridine in CYP2D6 poor metabolizers is approximately 50% of plasma clearance in subjects who are nonpoor CYP2D6 metabolizers [See Pharmacogenomics (12.5)]. In healthy subjects CYP2D6 poor metabolizers (n=4) given a single 0.25 mg dose of OLINVYK after 5 days of Itraconazole 200 mg QD (a strong CYP3A4 inhibitor), the total exposure (AUC) of OLINVYK was increased by approximately 80%; however, the peak concentration was not significantly affected [See Pharmacogenomics (12.5)]. The mean clearance of oliceridine was reduced to approximately 30% of that observed in nonpoor metabolizers of CYP2D6 [see Drug Interactions (7)].

12.5 Pharmacogenomics
Oliceridine is metabolized by polymorphic enzyme CYP2D6. CYP2D6 poor metabolizers have little to no enzyme activity. Approximately 3 to 10% of Whites, 2 to 7% of African Americans, and <2% of Asians, generally lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. In healthy subjects who are CYP2D6 poor metabolizers, the AU0-inf of oliceridine was approximately 2-fold higher than in subjects who are nonpoor CYP2D6 metabolizers. [See Warnings and Precautions (5.6), Use in Specific Populations (8.6)].

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<td>203585, 11/26/2019</td>
<td>Omacetaxine</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES The efficacy of SYNRIBO was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+]) (whether lost or never achieved); or no major cytogenetic response (MCR) by 52 weeks (i.e., ≥35% Ph+) (whether lost or never achieved); or progressive leukocytosis. (See Table 5)</td>
</tr>
<tr>
<td>207931, 07/23/2018</td>
<td>Ombitasvir, Paritaprevir, and Ritonavir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Clinical Trial Results in Adults with Chronic GT4 HCV Infection without Cirrhosis (...): HCV GT4-infected subjects had a median age of 51 years (range: 19 to 70); 64% were treatment-naïve, 17% were prior pegIFN/RBV null responders; 7% were prior pegIFN/RBV partial responders, 13% were prior pegIFN/RBV relapers; 65% were male; 9% were Black; 14% had a body mass index at least 30 kg/m²; 70% had baseline HCV RNA levels at least 800,000 IU/mL; 70% had IL28B (rs12979860) non-CC genotype; 7% had bridging fibrosis (F3). (...): 14.3 Clinical Trial Results in Adults with Chronic GT4 HCV Infection with Compensated Cirrhosis (...) Of the 59 subjects in the 12 week arm, median age was 56 years (range: 43 to 81); 51% were treatment-naïve, 29% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 12% were prior pegIFN/RBV relapers; 76% were male; 17% were Black; 29% had a body mass index of at least 30 kg/m²; 76% had baseline HCV RNA levels of at least 800,000 IU per mL; 86% had IL28B (rs12979860) non-CC genotype; 12% had platelet counts of less than 90 x 10⁹ per L; and 5% had albumin less than 3.5 mg per dL. (…)</td>
</tr>
<tr>
<td>020206, 08/21/2018</td>
<td>Omeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS Tacrolimus Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3)</td>
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<td>020007, 03/08/2017</td>
<td>Ondansetron</td>
<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolisers of CYP2D6 and those who were extensive metabolisers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo. (…)</td>
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| 208065, 12/18/2020                     | Osimertinib   | Oncology          | EGFR       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE

1.2 Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated as adjuvant therapy after tumor resection for patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)].

1.3 First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC

TAGRISSO is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)].

1.4 Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC

TAGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens [see Clinical Studies (14)].

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens [see Clinical Studies (14)]. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TAGRISSO following progression on or after EGFR TKI therapy based on the presence of an EGFR T790M mutation in tumor or plasma specimens [see Clinical Studies (14)]. Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

(….) The data in the Warnings and Precautions sections reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials [ADAURA (n=337), FLAURA (n=279), and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) [see Warnings and Precautions (5)].

The data described below reflect exposure to TAGRISSO (80 mg daily) in 337 patients with EGFR mutation-positive resectable NSCLC, and 558 patients with EGFR mutation-positive metastatic NSCLC in three randomized, controlled trials [ADAURA (n=337), FLAURA (n=279), and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiodermopathy that required steroid treatment, severe arrhythmia or baseline QTc interval greater than 470 msecs on electrocardiogram were excluded from enrollment in these studies. (…) Adjuvant Treatment of EGFR Mutation-Positive NSCLC

The safety of TAGRISSO was evaluated in ADAURA, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 22.5 months. (…) Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. (See Tables 4 and 5) (…) Previously Treated EGFR T790M Mutation-Positive Non-Small-Cell Lung Cancer

The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGFR T790M mutation-positive NSCLC who had progressive disease following first line EGFR TKI treatment. (…) Previously Treated EGFR T790M Mutation-Positive Non-Small Cell Lung Cancer

14 CLINICAL STUDIES

14.1 Adjuvant Treatment of Early-Stage EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

The efficacy of TAGRISSO was demonstrated in a randomized, double-blind, placebo-controlled trial (ADAURA (NCT02551106)) for the adjuvant treatment of patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. Eligible patients with resectable tumors (stage IIB – IIIA according to American Joint Commission on Cancer (AJCC) 7th edition) were required to have predominantly non-squamous histology and EGFR exon 19 deletions or exon 21 L858R mutations identified prospectively from tumor tissue in a central laboratory by the cobas® EGFR Mutation Test. Patients with clinically significant uncontrolled cardiac disease, prior history of ILD/pneumonitis, or who received treatment with any EGFR kinase inhibitor were not eligible for the study.

Patients were randomly assigned (1:1) to receive TAGRISSO 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy if given. Patients who did not receive adjuvant chemotherapy were randomized within 10 weeks and patients who received adjuvant chemotherapy were randomized within 28 weeks following surgery. Randomization was stratified by mutation type (exon 19 deletions or exon 21 L858R mutations), race (Asian or non-Asian) and tumor stage at diagnosis (II or IIIA) according to AJCC 7th edition. Treatment was given for 3 years or until disease recurrence, or unacceptable toxicity. The major efficacy outcome measure was disease-free survival (DFS, defined as reduction in the risk of disease recurrence or death) in patients with stage II – IIIA NSCLC determined by investigator assessment. Additional efficacy outcome measures included DFS in the overall population (patients with stage II – IIIA NSCLC), and overall survival (OS) in patients with stage II – IIIA NSCLC and in the overall population. A total of 662 patients were randomized to 2 treatment groups.

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</table>
| 203505, 01/23/2019 | Ospemifene (1) | Gynecology | CYP2C9 | Clinical Pharmacology | **12 CLINICAL PHARMACOLOGY**  
12.3 Pharmacokinetics  
*Drug Interactions*  
*Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug*  
**Warfarin**  
Ospemifene 60 mg was given after a light breakfast (two slices of bread with ham and cheese and juice) once daily for 12 days in sixteen postmenopausal women who were determined to be rapid metabolizers of CYP2C9 (CYP2C9*1/*1 or CYP2C9*1/*2). On Day 8, a single dose of warfarin 10 mg and vitamin K 10 mg were administered one hour after a light breakfast. The geometric mean ratio (90% CI) for hydroxybupropion, an active metabolite formed via CYP2B6, with and without ospemifene for Cmax and AUC0-inf were 1.16 (1.09-1.24) and 0.98 (0.92-1.04), respectively. Multiple doses of ospemifene did not significantly affect the pharmacokinetics of a single dose of warfarin. No study was conducted with multiple doses of warfarin. |
| 203505, 01/23/2019 | Ospemifene (2) | Gynecology | CYP2B6 | Clinical Pharmacology | **12 CLINICAL PHARMACOLOGY**  
12.3 Pharmacokinetics  
*Drug Interactions*  
*Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug*  
**Bupropion**  
Ospemifene 60 mg was administered once daily for seven consecutive days after the evening meal in sixteen postmenopausal women (not homozygous for CYP2B6*6). On Day 8, a single 150 mg dose of sustained release bupropion was administered in morning under fasted condition. The geometric mean ratio (90% CI) for bupropion with and without ospemifene for Cmax and AUC0-inf were 0.82 (0.75-0.91) and 0.81 (0.77-0.86), respectively. The geometric mean ratio (90% CI) for hydroxybupropion, an active metabolite formed via CYP2B6, with and without ospemifene for Cmax and AUC0-inf were 1.16 (1.09-1.24) and 0.98 (0.92-1.04), respectively. |
| 202810, 12/13/2018 | Oxcarbazepine | Neurology | HLA-B | Warnings and Precautions | **5 WARNINGS AND PRECAUTIONS**  
5.4 Serious Dermatological Reactions  
Association with HLA-B*1502  
Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN with Ostellar XR treatment. Human Leukocyte Antigen (HLA) allele B*1502 increases the risk for developing SJS/TEN in patients treated with carbamazepine. The chemical structures of immediate release oxcarbazepine and Ostellar XR are similar to that of carbamazepine. Available clinical evidence, and data from nonclinical studies showing a direct interaction between immediate release oxcarbazepine and HLA-B*1502 protein, suggest that the HLAB*1502 allele may also increase the risk for *Therapeutic areas do not necessarily reflect the CDER review division.  
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| **208032, 11/02/2018**                | Oxymetazoline and Tetracaine (1) | Anesthesiology | G6PD | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Methemoglobinemia  
Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…) |
| **208032, 11/02/2018**                | Oxymetazoline and Tetracaine (2) | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Methemoglobinemia  
Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue KOVANAZE and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. |
| **207103, 09/09/2019**                | Palbociclib (1) | Oncology | ESR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer for initial endocrine based therapy  
• an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or  
• fulvestrant in patients with disease progression following endocrine therapy.  

6 ADVERSE REACTIONS  
6.1 Clinical Studies Experience  
Study 1: IBRANCE plus Letrozole  
Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy  
The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months. (…)  
Study 2: IBRANCE plus Fulvestrant  
Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy  
The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months. (…)  
Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer  
Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.  

14 CLINICAL STUDIES  
Study 1: IBRANCE plus Letrozole  
Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy  

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| 207103, 09/09/2019                      | Palbociclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE

IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or
- fulvestrant in patients with disease progression following endocrine therapy.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Studies Experience

#### Study 1: IBRANCE plus Letrozole

**Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy**

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months. (…)

**Study 2: IBRANCE plus Fulvestrant**

**Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy**

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months. (…)

Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer

Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.

#### 14 CLINICAL STUDIES

**Study 1: IBRANCE plus Letrozole**

**Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy**

Study 1 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. (…)

**Study 2: IBRANCE plus Fulvestrant**

**Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy**

Study 2 (PALOMA-3) was an international, randomized, double-blind, parallel group, multicenter study of IBRANCE plus fulvestrant versus placebo plus fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…)

| 021999, 01/25/2019 | Paliperidone | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Metabolism and Elimination

Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. (…)

| 021372, 09/18/2014 | Palonosetron | Gastroenterology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-Hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT3 receptor antagonistic activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

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<td>6 ADVERSE REACTIONS</td>
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<td>Panitumumab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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1.1 Metastatic Colorectal Cancer

Vectibix is indicated for the treatment of patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) [see Dosage and Administration (2.1)]:
• As first-line therapy in combination with FOLFOX [see Clinical Studies (14.2)]
• As monotherapy following disease progression after prior treatment with fluoropyrimidines, oxaliplatin, and irinotecan-containing chemotherapy [see Clinical Studies (14.1)].

Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown [see Dosage and Administration (2.1), Warnings and Precautions (5.2), and Clinical Pharmacology (12.1)].

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection

Prior to initiation of treatment with Vectibix, assess RAS mutational status in colorectal tumors and confirm the absence of a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of both KRAS and NRAS. Information on FDA-approved tests for the detection of RAS mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/CompanionDiagnostics.

5 WARNINGS AND PRECAUTIONS
5.2 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with RAS-Mutant mCRC

Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereafter is referred to as ‘‘RAS’’ [see Indications and Usage (1.1), Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14)].

Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of RAS mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing RAS mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents [see Indications and Usage (1.1), and Clinical Pharmacology (12.1)].

Additionally, in Study 20050203, 272 patients with RAS-mutant mCRC tumors received Vectibix in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with RAS-mutant mCRC who received Vectibix and FOLFOX versus FOLFOX alone [see Indications and Usage (1.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:
• (…) Increased Tumor Progression, Increased Mortality, or Lack of Benefit in RAS-Mutant mCRC [see Indications and Usage (1.1) and Warnings and Precautions (5.2)] (…)

6.1 Clinical Trials Experience

(…) Safety data are presented from two clinical trials in which patients received Vectibix: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 20050203 are limited to 656 patients with wild-type KRAS mCRC. The safety profile of Vectibix in patients with wild-type RAS mCRC is similar with that seen in patients with wild-type KRAS mCRC.

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**14.1 Recurrent or Refractory mCRC**

The safety and efficacy of Vectibix was demonstrated in Study 20020408, an open-label, multinational, randomized, controlled trial of patients with EGFR-expressing, metastatic carcinoma of the colon or rectum, and in Study 20080763, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type KRAS mCRC, and in Study 20100007, an open-label, multicenter, multinational, randomized trial of 377 patients with wild-type KRAS mCRC. (…) Study 20020408 (NCT00113763) (…) The study results were analyzed in the wild-type KRAS subgroup where KRAS status was retrospectively determined using archived paraffin-embedded tumor tissue. KRAS mutation status was determined in 427 patients (92%) of these, 243 (57%) had no detectable KRAS mutations in either codons 12 or 13. The hazard ratio for PFS in patients with wild-type KRAS mCRC was 0.45 (95% CI: 0.34-0.59) favoring the panitumumab arm. The response rate was 17% for the panitumumab arm and 0% for BSC. There were no differences in OS; 77% of patients in the BSC arm received panitumumab at the time of disease progression. Study 20080763 (NCT00101377)

Study 20080763 was an open-label, multicenter, multinational, randomized (1:1) clinical trial stratified by region (North America, Western Europe, and Australia versus rest of the world) and ECOG PS (0 and 1 vs 2) in patients with wild-type KRAS mCRC. (See Table 3 and Figure 1) (…) Study 20100007 (NCT01413295) Study 20100007 was an open-label, multicenter, randomized (1:1) clinical study stratified by ECOG performance status (0 or 1 vs 2) and region (sites in Europe versus Asia versus rest of world) in patients with wild-type KRAS mCRC. Eligible patients were required to have received prior therapy with 5-fluorouracil, oxaliplatin, and a thymidylate synthase inhibitor; and have wild-type KRAS exon 2 mCRC as determined by a clinical trial assay. An assessment for RAS status (defined as KRAS exons 2, 3, and 4 and NRAS exons 2, 3, and 4) using Sanger sequencing was conducted in patients for whom tumor tissue was available. Patients were randomized to receive Vectibix (6 mg/kg intravenously every 14 days) plus BSC or BSC alone. Patients received Vectibix and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. Median OS was 13.9 months (95% CI: 12.0, 15.6) among patients with wild-type KRAS mCRC. Secondary efficacy outcome measures included OS in the subgroup of patients with wild-type RAS mCRC, PFS and ORR in patients with wild-type KRAS; and PFS and ORR in the subgroup of patients with wild-type RAS mCRC. (…) KRAS tumor mutation status was available for all patients and RAS tumor mutation status was available for 86% of the 377 patients. Among the 377 patients, 270 (72%) patients had wild-type RAS tumors, 54 (14%) had mutant RAS tumors, and 54 (14%) had unknown RAS tumor status. (See Table 4 and Figure 2).

**14.2 First-line in Combination with FOLFOX Chemotherapy**

(…) The prespecified major efficacy measure was PFS in patients (n = 656) with wild-type KRAS mCRC as assessed by a blinded independent central review of imaging. Other key efficacy measures included OS and ORR. In Study 20050203, in the wild-type KRAS subgroup (n = 656), 64% of patients were men, 92% White, 2% Black, and 4% Hispanic or Latino. Sixty-six percent of patients had colon cancer and 34% had rectal cancer. ECOG performance was 0 in 38% of patients, and 2 in 6% of patients. Median age was 61.5 years. The efficacy results in Study 20050203 in patients with wild-type KRAS mCRC are presented in Table 5 below. (See Table 5) (…) Exploratory Analysis of OS

An exploratory analysis of OS was performed in 82% of patients with wild-type KRAS mCRC. Eligible patients were required to have received prior therapy with 5-fluorouracil, oxaliplatin, and a thymidylate synthase inhibitor, and have wild-type KRAS exon 2 mCRC as determined by a clinical trial assay. An assessment for RAS status was conducted in patients for whom tumor tissue was available. Patients were randomized to receive Vectibix (6 mg/kg intravenously every 14 days) plus BSC or BSC alone. Patients received Vectibix and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. Median OS was 13.9 months (95% CI: 12.0, 15.6) among patients with wild-type KRAS mCRC. Secondary efficacy outcome measures included OS in the subgroup of patients with wild-type RAS mCRC, PFS and ORR in patients with wild-type KRAS; and PFS and ORR in the subgroup of patients with wild-type RAS mCRC. (…) KRAS tumor mutation status was available for all patients and RAS tumor mutation status was available for 86% of the 377 patients. Among the 377 patients, 270 (72%) patients had wild-type RAS tumors, 54 (14%) had mutant RAS tumors, and 54 (14%) had unknown RAS tumor status. (See Table 4 and Figure 2).

**14.3 RAS-Mutant mCRC**

Vectibix is not effective for the treatment of patients with RAS-mutant mCRC, defined as a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), or exon 4 (codons 117 and 146) of KRAS and NRAS. In Study 20050203, among patients with RAS-mutant tumors, the median PFS was 7.3 months (95% CI: 6.3, 7.9) among 274 patients receiving Vectibix plus FOLFOX and 8.7 months (95% CI: 7.6, 9.4) among patients who received FOLFOX alone (HR = 1.31, 95% CI: 1.07, 1.60). The median OS was 15.6 months.

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<td>020987, 04/25/2019</td>
<td>Pantoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>Patients with Hepatic Impairment</td>
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<td>In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Doses higher than 40 mg/day have not been studied in hepatically impaired patients.</td>
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<tr>
<td>125511, 12/17/2018</td>
<td>Parathyroid Hormone</td>
<td>Inborn Errors of Metabolism</td>
<td>CASR</td>
<td>1 INDICATIONS AND USAGE</td>
<td>NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.</td>
</tr>
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<td></td>
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<td>Because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone [see Warnings and Precautions (5.1)].</td>
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<tr>
<td></td>
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<td>NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.</td>
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<td>NATPARA was not studied in patients with acute post-surgical hypoparathyroidism.</td>
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<tr>
<td>020031, 01/04/2017</td>
<td>Paroxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>DRUG INTERACTIONS</td>
<td>Drugs Metabolized by CYP2D6:</td>
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<td>(…) In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine Cmax values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine. (…)</td>
</tr>
<tr>
<td>210922, 08/10/2018</td>
<td>Patisiran</td>
<td>Neurology</td>
<td>TTR</td>
<td>6 ADVERSE REACTIONS</td>
<td>(…) At baseline, 46% of patients were in Stage 1 of the disease and 53% were in Stage 2. Forty-three percent of patients had Val30Met mutations in the transhyretin gene; the remaining patients had 38 other point mutations. Sixty-two percent of ONPATTRO-treated patients had non-Val30Met mutations, compared to 48% of the placebo-treated patients. (…)</td>
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<tr>
<td>022465, 06/02/2020</td>
<td>Pazopanib (1)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.2 Pharmacodynamics</td>
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<td>14 CLINICAL STUDIES</td>
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<td>125293, 07/07/2022</td>
<td>Pegloticase</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions, Adverse Reactions, Patient Counseling Information</td>
<td>BOXED WARNING: WARNING: ANAPHYLAXIS and INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA. (…) Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency (4, 5.3).</td>
</tr>
<tr>
<td>125514, 12/15/2023</td>
<td>Pembrolizumab (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (plumumab-Referactory Melanoma) The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. (…)</td>
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<td>125514, 12/15/2023</td>
<td>Pembrolizumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>(…A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease, 66% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IFO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (41%) were previously treated with a BRAF inhibitor. (…) (ipilimumab-Refractory Melanoma) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated ≥110% ULN) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. (…) Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease. (…) (PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations, and is: • stage III where patients are not candidates for surgical resection or definitive chemoradiation, or • metastatic. KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR or ALK genomic tumor aberrations. KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. KEYTRUDA, in combination with platinum-containing chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after platinum-containing chemotherapy, Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after platinum-containing chemotherapy, Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC whose tumors express PD-L1 (Combined Positive Score (CPS) ≥1) as determined by an FDA-approved test [see Dosage and Administration (2.1)]. KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC whose tumors express PD-L1 (Combined Positive Score (CPS) ≥1) as determined by an FDA-approved test [see Dosage and Administration (2.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test [see Dosage and Administration (2.1)].)</td>
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represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.

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(...)

(…) The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

The study population characteristics were: median age of 54 years (range: 19 to 88); 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage II, 18% had stage IIA, 46% had stage IIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage III ([4+ positive lymph nodes]; 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IUCO assay. (…) For patients with PD-L1 positive tumors, the HR was 0.54 (95% CI: 0.42, 0.69); p<0.001. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic non-squamous NSCLC with pembrolizumab and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pembrolizumab and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02576860), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cispain vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). (…) The study population characteristics were: median age of 64 years (range: 34 to 84); 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG performance status of 1; and 16% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% [negative]. (See Table 21) (…) First-line treatment of metastatic squamous NSCLC with carboplatin and paclitaxel chemotherapy

The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel chemotherapy was investigated in KEYNOTE-040 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS<1% [negative] vs. TPS ≥1%). (…) Seventy-two percent had tumor PD-L1 expression TPS ≥1% [positive]. (See Table 22) (…) First-line treatment of metastatic non-squamous NSCLC with pemetrexed and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 559 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS<1% [negative] vs. TPS ≥1%). (…) Seventy-five percent had tumor PD-L1 expression TPS ≥1% [positive]. (See Table 23) (…) First-line treatment of metastatic NSCLC as a single agent KEYNOTE-042

The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multi-center, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 HAC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥50% vs. TPS 1%-49%). (…) The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 37 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%. (See Table 37) (…) The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥50% NSCLC were intermediate between the results of those with PD-L1 TPS ≥20% and those with PD-L1 TPS ≥1%. In a pre-specified exploratory subgroup analysis for patients with TPS ≥1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11). (KEYNOTE-024

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The efficacy of KEYTRUDA was also investigated in KEYNOTE-042 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were eligible. (…) Previously treated NSCLC The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01985857), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS<1-49%), ECOG PS (0 vs. 1), and geographic region (East Asia vs. non-East Asia). (…) The study population characteristics were: median age of 63 years (range: 20 to 88); 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. (…) 14.4 Head and Neck Squamous Cell Cancer First-line treatment of metastatic or unresectable, recurrent HNSCC The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 382 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the PD-L1 IHC 22C3 pharmDx kit, ECOG PS status (0 vs. 1). (…) A retrospective re-classification of patients' tumor PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx kit was conducted using the tumor specimens used for randomization. (…) The study population characteristics were: median age of 61 years (range: 20 to 94); 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS <50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20. (…) The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. (…) In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab with chemotherapy were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI:0.51, 0.94). 14.7 Urothelial Carcinoma Capstain ineligible Patients with Urothelial Carcinoma Among the 370 patients, 30% (n = 110) had tumors that expressed PD-L1 with a CPS ≥10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. The study population characteristics of these 110 patients were: median age of 73 years; 68% male; and 87% White. Eighty-two percent had M1 disease, and 18% had M0 disease. (See Table 46) (…) Previously Untreated Urothelial Carcinoma (…) The independent Data Monitoring Committee (IDMC) for the study conducted a review of early data and found that in patients classified as having low PD-L1 expression (CPS <10), those treated with KEYTRUDA monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The IDMC recommended to stop further accrual of patients with low PD-L1 expression in the monotherapy arm, however, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm. 14.8 Microsatellite Instability-High Cancer (See Table 49) 14.9 Gastric Cancer Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a CPS ≥1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. (…) 14.10 Esophageal Cancer KEYNOTE-181 The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. (…) The major efficacy outcome measure was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. (…) A total of 628 patients were enrolled and randomized to KEYTRUDA (n=314) or investigator's treatment of choice (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. (…) The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 52 and Figure 12 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10. * Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. 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| 12554 (3) | Pembrolizumab | Oncology | Microsatellite Instability, Mismatch Repair | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | **1 INDICATIONS AND USAGE**
1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

**KEYTRUDA** is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options [see Dosage and Administration (2.1)].

1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

**KEYTRUDA** is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test [see Dosage and Administration (2.1)].

1.15 Endometrial Carcinoma

**KEYTRUDA**, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [see Dosage and Administration (2.1)]. **KEYTRUDA**, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [see Dosage and Administration (2.1)].

**2 DOSAGE AND ADMINISTRATION**

2.1 Patient Selection

Information on FDA-approved tests for patient selection is available at: http://www.fda.gov/CompanionDiagnostics.

Patient Selection for Single-Agent Treatment

Select patients for treatment with **KEYTRUDA** as a single agent based on the presence of positive PD-L1 expression in:

- Stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation [see Clinical Studies (14.2)].
- metastatic NSCLC [see Clinical Studies (14.3)].
- first-line treatment of metastatic or unresectable, recurrent HNSCC [see Clinical Studies (14.3)].
- previously treated recurrent locally advanced or metastatic esophageal cancer [see Clinical Studies (14.10)].
- recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [see Clinical Studies (14.11)].

For the MSI-H/dMMR indications, select patients for treatment with **KEYTRUDA** as a single agent based on MSI-H/dMMR status in tumor specimens [see Clinical Studies (14.7, 14.8)].

For the TMB-H indication, select patients for treatment with **KEYTRUDA** as a single agent based on TMB-H status in tumor specimens [see Clinical Studies (14.7, 14.17)].

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Because subclonal dMMR mutations and microsatellite instability may arise in high-grade gliomas during temozolomide therapy, it is recommended to test for TMB-H, MSI-H, and dMMR in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Additional Patient Selection Information for MSI-H or dMMR in Patients with non-CRC Solid Tumors

Due to discordance between local tests and FDA-approved tests, confirmation of MSI-H or dMMR status is recommended by an FDA-approved test in patients with MSI-H or dMMR solid tumors, if feasible. If unable to perform confirmatory MSI-H/dMMR testing, the presence of TMB ≥10 mut/Mb, as determined by an FDA-approved test, may be used to select patients for treatment [see Clinical Studies (14.7)].

Patient Selection for Combination Therapy

For use of KEYTRUDA in combination with chemotherapy and trastuzumab, select patients based on the presence of positive PD-L1 expression (CPS ≥1) in locally advanced untreated or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma [see Clinical Studies (14.9)].

For use of KEYTRUDA in combination with chemotherapy, with or without bevacizumab, select patients based on the presence of positive PD-L1 expression in persistent, recurrent, or metastatic cervical cancer [see Clinical Studies (14.11)].

For the pMMR/not MSI-H advanced endometrial carcinoma indication, select patients for treatment with KEYTRUDA in combination with lenvatinib based on MSI or MMR status in tumor specimens [see Clinical Studies (14.16)].

For use of KEYTRUDA in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression in locally recurrent untreated or metastatic TNBC [see Clinical Studies (14.19)].

Additional Patient Selection Information

An FDA-approved test for the detection of not MSI-H is currently unavailable for the selection of patients with not MSI-H endometrial carcinoma for treatment with KEYTRUDA in combination with lenvatinib [see Clinical Studies (14.16)].

2.2 Recommended Dosage

See Table 1

6 ADVERSE REACTIONS

**Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer**

Among the 153 patients with MSI-H or dMMR CRC enrolled in KEYNOTE-177 [see Clinical Studies (14.9)] treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 30.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in 2799 patients with metastatic or NSCLC treated with KEYTRUDA as a single agent.

**Endometrial Carcinoma**

The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings [see Clinical Studies (14.15)]. Patients with endometrial carcinoma that is not MSI-H or dMMR received KEYTRUDA 200 mg every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

For patients with not MSI-H or dMMR tumor status, the median duration of study treatment was 7.2 months (range: 1 day to 26.8 months) and the median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day to 25.8 months). (See Tables 35 and 36) (…)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with HL, PMBCL, MCC, MSI-H cancer, and TMB-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.4, 14.5, 14.7, 14.13, 14.16)] (…)

14 CLINICAL STUDIES

14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The eficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. (See Table 59) (…)

A total of 149 patients with MSI-H or dMMR cancers were identified across the five trials. Among these 149 patients, the baseline characteristics were: median age of 55 years, 36% age 65 or older; 56% male; 77% White, 19% Asian, and 2% Black; and 36% ECOC PS of 0 and 64% ECOC PS of 1. Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 419 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

Efficacy results are summarized in Tables 57 and 58.

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain

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<td>Pembrolizumab</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. (See Table 59) (…)</td>
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14.9 Gastric Cancer
First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

(…) At the time of the interim analysis, ORR and DoR were assessed in the first 264 patients randomized. Among the 264 patients, the population characteristics were: median age of 65 years (range: 19 to 84); 41% age 65 or older; 82% male; 63% White; 31% Asian, and 0.8% Black; 47% ECOG PS of 0 and 53% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (stage IV) and 3% had locally advanced unresectable disease. Eighty-seven percent had tumors that expressed PD-L1 with a CPS ≥1. Ninety-one percent (n=240) had tumors that were not MSI-H, 1% (n=2) had tumors that were MSI-H, and in 8% (n=22) the status was not known. Eighty-seven percent of patients received CAPOX. Previously Treated Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a CPS ≥1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDX kit. The baseline characteristics of these 143 patients were: median age of 64 years, 47% age 65 or older; 77% male; 82% White and 11% Asian; and 43% ECOG PS 0 of 0 and 57% ECOG PS of 1. Eighty-five percent had M1 disease and 7% had M0 disease. Fifty-one percent had two or 49% had three or more prior lines of therapy in the recurrent or metastatic setting. (…) |

14.15 Endometrial Carcinoma
Patients with endometrial carcinoma that were not MSI-H or dMMR were stratified by ECOG performance status, geographic region, and history of pelvic radiation. (…) Efficiency results for the 143 patients with ECOG performance status that were MSI-H or dMMR are presented in Table 67 and Figures 17 and 18. (See Table 67 and Figures 17 and 18) (…) |

1.2 Non-Small Cell Lung Cancer
Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. (See Table 59) (…) |

6.1 Clinical Trials Experience
NSCLC
First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and investigator’s choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (1:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.2)]. (…) |

Previously Untreated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC [see Clinical Studies (14.2)]. Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator’s choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease or a medical condition that required systemic therapy within 2 years of treatment; a medical condition that required systemic therapy within 1 year of treatment; a medical condition that required systemic therapy within 1 year of treatment; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. (…) |

Previously Treated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations [see Clinical Studies (14.2)]. |

14 CLINICAL STUDIES
14.2 Non-Small Cell Lung Cancer
First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. (…) |

First-line treatment of metastatic NSCLC with KEYTRUDA

KEYNOTE-042

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| 125514, 12/15/2023                    | Pembrolizumab | Oncology | ALK | Indications and Usage, Adverse Reactions, Clinical Studies | The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. (…)

Previous treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. (…)

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<td>Pembrolizumab</td>
<td>Oncology</td>
<td>Tumor Mutational Burden</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) ≥10 mutations/megabase (mut/Mb) solid tumors, as determined by an FDA-approved test [see Dosage and Administration (2.1)], that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.16)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.</td>
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<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.9)]. Continued approval of this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.</td>
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**Gastric Cancer**

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric Cancer with Trastuzumab and Chemotherapy

The safety analysis of Study KEYNOTE-811 included 217 patients with HER2-positive gastric cancer who received KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=180) or FP (n=28) every 3 weeks, compared to 216 patients who received placebo, trastuzumab, and CAPOX (n=187) or FP (n=29) every 3 weeks [see Clinical Studies (14.9)]. (…)

14 CLINICAL STUDIES

14.9 Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in Study KEYNOTE-811 (NCT03615328), a multicenter, randomized, double-blind, placebo-controlled trial that was designed to enroll 652 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥1 or CPS <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). (…)

Previously treated Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma. The efficacy of KEYTRUDA was investigated in KEYNOTE-059 (NCT02335411), a multicenter, non-randomized, open-label multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy. (…)

14.10 Esophageal Cancer

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer KEYNOTE-181

The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with a history of non-responding pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppressive therapy were excluded. (…)

6 ADVERSE REACTIONS

Non-Squamous NSCLC

First-line Treatment of Metastatic Non-squamous NSCLC with Pembrolizumab and Platinum Chemotherapy. The safety of ALIMTA, in combination with pembrolizumab and investigator’s choice of platinum (either carboplatin or cisplatin), was investigated in Study KEYNOTE-189, a multicenter, double-blind, randomized, active-controlled trial conducted in patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. A total of 607 patients received ALIMTA, pembrolizumab, and platinum every 3 weeks for 4 cycles followed by ALIMTA and pembrolizumab (n=405), or placebo, ALIMTA, and platinum every 3 weeks for 4 cycles followed by placebo and ALIMTA (n=202). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible [see Clinical Studies (14.1)].

14 CLINICAL STUDIES

14.1 Non-Squamous NSCLC

Initial Treatment in Combination with Pembrolizumab and Platinum. The efficacy of ALIMTA in combination with pembrolizumab and platinum chemotherapy was investigated in Study KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in patients with metastatic non-squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never versus former/current), choice of platinum (cisplatin versus carboplatin), and tumor PD-L1 status (TPS ≤1% [negative] versus TPS >1%). Patients were randomized (2:1) to one of the following treatment arms: (…)

021462, 08/31/2022

Pemetrexed (1) Oncology ALK Indications and Usage, Adverse Reactions, Clinical Studies

1 INDICATIONS AND USAGE

1.1 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

ALIMTA® is indicated:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. (…)

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer [see Clinical Studies (14.1)].

021462, 08/31/2022

Pemetrexed (2) Oncology EGFR Indications and Usage, Adverse Reactions, Clinical Studies

1 INDICATIONS AND USAGE

1.1 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

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| Pemigatinib (1) | Oncology | FGFR1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE  
1.2 Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement  
PEMAZYRE is indicated for the treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLN) with fibroblast growth factor receptor 1 (FGFR1) rearrangement. |
| Pemetrexed (3) | Oncology | CD274 (PD-L1) | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Non-Squamous NSCLC  
Initial Treatment in Combination with Pemetrexed and Platinum  
The efficacy of ALIMTA in combination with pemetrexed and platinum chemotherapy was investigated in Study KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in patients with metastatic non-squamous NSCLC. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never versus former/current), choice of platinum (cisplatin versus carboplatin), and tumor PD-L1 status (TPS <1% [negative] versus TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms: (…) |

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| 05/10/2002                             |      |                   |            |                   | The pooled safety population described in the WARNINGS AND PRECAUTIONS section reflects exposure to PEMAZYRE at a starting dose of 13.5 mg orally once daily (intermittent or continuous administration) in 635 patients with advanced malignancies. Among the 635 patients, 31% were exposed for 6 months or longer, and 11% were exposed greater than one year, including patients with previously treated, advanced, or metastatic cholangiocarcinoma in FIGHT-202 and patients with MLNs with FGFR1 rearrangement in FIGHT-203. Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement FIGHT-203 The safety of PEMAZYRE was evaluated in FIGHT-203, which included 34 patients who were treated for MLN with FGFR1 rearrangement [see Clinical Studies (14.2)]. Patients were treated with PEMAZYRE 13.5 mg once daily on a continuous schedule (the approved recommended starting dosage) or for 14 days on follow by 7 days off therapy (an unapproved dosage regimen in MLN with FGFR1 rearrangement) until disease progression, unacceptable toxicity, or they were able to receive allogeneic stem cell transplant. The median duration of treatment was 205 days (range: 30-1347 days). (...) 8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use In FIGHT-202 in patients with cholangiocarcinoma, 32% of patients were 65 years and older, and 8% of patients were 75 years and older. In FIGHT-203 in patients with MLN with FGFR1 rearrangement, 44% of patients were 65 years and older, and 2.9% of patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. 14 CLINICAL STUDIES 14.2 Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement FIGHT-203 (NCT03011372), a multicenter open-label, single-arm trial, evaluated the efficacy of PEMAZYRE in 28 patients with MLNs with FGFR1 rearrangement. Inclusion criteria included documented myeloid/lymphoid neoplasms with FGFR1 rearrangement, patients could have relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT) or after a disease modifying therapy, or were not a candidate for allo-HSCT or other disease modifying therapies. Patients received PEMAZYRE 13.5 mg once daily in 21-day cycles, either on a continuous schedule (the approved recommended starting dosage) or as an intermittent schedule (14 days on, 7 days off, an unapproved dosage regimen in MLN with FGFR1 rearrangement). PEMAZYRE was administered until disease progression or unacceptable toxicity or until patients were able to receive allo-HSCT. The median age was 65 years (range: 39-78), 64% were female, 68% were White, 3.6% were Black or African American, 11% were Asian, 3.6% were American Indian/Alaska Native 3.6% were other race, and race was unknown or not collected for 11% of patients; 3.6% were Hispanic, 68% were not Hispanic, 11% were other ethnicity, and ethnicity was not reported in 18%, and 88% had an ECOG performance status of 0 or 1. (...) 14.1 Cholangiocarcinoma PEMAZYRE is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). 2.1 Patient Selection Select patients for the treatment of locally advanced or metastatic cholangiocarcinoma with PEMAZYRE based on the presence of an FGFR2 fusion or rearrangement as detected by an FDA-approved test [see Clinical Studies (14.1)]. Information on FDA-approved test(s) for the detection of an FGFR2 fusion or rearrangement in cholangiocarcinoma is available at http://www.fda.gov/CompanionDiagnostics. 2.3 Dosage Modification for Adverse Reactions The recommended dose reductions for adverse reactions are provided in Table 1. 14 CLINICAL STUDIES 14.1 Cholangiocarcinoma FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial, evaluated the efficacy of PEMAZYRE in 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least 1 prior therapy and who had an FGFR2 gene fusion or non-fusion rearrangement, as determined by a clinical trial assay performed at a central laboratory. Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene leaving the FGFR2 kinase domain intact. (...) The median age was 56 years (range: 26 to 77 years), 61% were female, 74% were White, and 95% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42%) or 1 (55%). Ninety-eight percent of patients had intrahepatic cholangiocarcinoma. Eighty-six percent of patients had in-frame FGFR2 gene fusions and the most commonly identified FGFR2 fusion was FGFR2-BICC1 (34%). Fourteen percent of patients had other FGFR2 rearrangements that could not be confidently predicted to be in-frame fusions, including rearrangements without an identifiable partner gene. All patients had received at least 1 prior line of systemic therapy, 27% had 2 prior lines of therapy, and 12% had 3 or more prior lines of therapy. Ninety-six percent of patients had received prior platinum-based therapy including 76% with prior gemcitabine/cisplatin. | 2023-09-16 | Pemigatinib (2) | Oncology | FGFR2 | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE 1.1 Cholangiocarcinoma PEMAZYRE is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. 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<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>Metabolism of a number of medications, including antipsychotics, antidepressants, b-blockers, and antiarrhythmics, occurs through the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called “poor” metabolizers. Among other populations the prevalence is not known. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. In one study of 45 elderly patients suffering from dementia treated with perphenazine, the 5 patients who were prospectively identified as poor P450 2D6 metabolizers had reported significantly greater side effects during the first 10 days of treatment than the 40 extensive metabolizers, following which the groups tended to converge. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events. (…)</td>
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12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
(…) The pharmacokinetics of perphenazine covary with the hydroxylation of debrisoquine which is mediated by cytochrome P450 2D6 (CYP 2D6) and thus is subject to genetic polymorphism - ie, 7%-10% of Caucasians and a low percentage of Asians have little or no activity and are called “poor” metabolizers. “Poor metabolizers of CYP 2D6 will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or “extensive” metabolizers. (…) |

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<td><strong>14.1 Metastatic Breast Cancer</strong></td>
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| 14.1.1 Neoadjuvant Treatment of Breast Cancer NeoSphere | Oncology          | ESR, PGR (Hormone Receptor) | Clinical Studies | (prior or prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment. (…)
|                                            |                   |            |                   |                |
| 14.1.2 Neoadjuvant Treatment of Breast Cancer NeoSphere |                   |            |                   |                |
| 14.2 Neoadjuvant Treatment of Breast Cancer NeoSphere |                   |            |                   |                |
| 14.3 Adjuvant Treatment of Breast Cancer APHINITY (NCT01358877) |                   |            |                   |                |
| 14.1 Metastatic Breast Cancer             |                   |            |                   |                |
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|                                            |                   |            |                   |                |
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| 008762, 02/16/2021 | Phenytoin (1) | Neurology | CYP2C9 | Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS

5.3 Serious Dermatologic Reactions DILANTIN can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.4)]. The onset of symptoms is usually within 28 days, but can occur later. DILANTIN should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCArs.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding DILANTIN as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)].

The use of HLA-B*1502 or CYP2C9 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the use of dermatologic monitoring have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.7 Use in Patients with Decreased CYP2C9 Function Patients who are intermediate or poor metabolizers of CYP2C9 substrates (e.g., *1/*3, *2/*2, *3/*3) may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers (e.g., *1/*1). Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses of phenytoin to maintain similar steady-state concentrations compared to normal metabolizers. If early signs of dose-related central nervous system (CNS) toxicity develop, serum concentrations should be checked immediately [see Clinical Pharmacology (12.5)].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

12.5 Pharmacogenomics

CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate (e.g., *1/*3, *2/*2) or poor metabolism (e.g., *2/*3, *3/*3) have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also be in decrease clearance of phenytoin (e.g., *5, *6, *8, *11). The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2-3% in the White population, 5.4% in the Asian population, and 1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-36% in the Asian population [see Warnings and Precautions (5.3) and Use in Specific Populations (8.7)].

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<td>5.2 Ototoxicity</td>
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<td></td>
<td></td>
<td>Ototoxicity with use of ZEMDRI. Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported with ZEMDRI. Symptoms of aminoglycoside-associated ototoxicity may be irreversible and may not become evident until after completion of therapy. Regarding the incidence of adverse reactions associated with cochlear or vestibular function, in Trial 1, there was one case of reversible hypoacusis (1/303;0.3%) in ZEMDRI-treated patients and one case of tinnitus (1/303;0.3%) in mepremep-treated patients [see Adverse Reactions (6.1)]. In Trial 2, one case each of irreversible tinnitus and reversible vertigo was reported in ZEMDRI-treated patients, and one case of an abnormal audiogram occurred in a levofloxacin-treated patient [see Adverse Reactions (6.1)]. Aminoglycoside-associated ototoxicity has been observed primarily in patients with a family history of hearing loss (excluding age-related hearing loss), patients with renal impairment, and in patients receiving higher doses and/or for longer periods than recommended. In Trial 1 and Trial 2, patients with a history of hearing loss, with the exception of age-related hearing loss, were excluded. The benefit-risk of ZEMDRI therapy should be considered in these patients. Risk of Ototoxicity Due to Mitochondrial DNA Variants Cases of ototoxicity with aminoglycosides have been observed in patients with certain variants in the mitochondrial encoded 12S rRNA gene (MT-RNR1), particularly the m.1555A&gt;G variant. Ototoxicity occurred in some patients when their aminoglycoside serum levels were within the recommended range. Mitochondrial DNA variants are present in less than 1% of the general US population, and the proportion of the variant carriers who may develop ototoxicity as well as the severity of ototoxicity is unknown. In case of known maternal history of ototoxicity due to aminoglycoside use or a known mitochondrial DNA variant in the patient, consider alternative treatments other than aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the severity of infection and lack of safe and effective alternative therapies.</td>
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<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.2 Venous Thromboembolism Venous thromboembolic events occurred in 6% (25/449) of Iclusig-treated patients, including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients) with vision loss. In the phase 2 trial, the incidence of venous thromboembolism was 9% (3/32) in patients with Ph+ ALL, 10% (6/62) in patients with blast phase (BP) CML, 4% (3/85) in patients with AP-CML, and 5% (13/270) in patients with CP-CML. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism [see Dosage and Administration (2.3)].</td>
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<td>5.4 Hepatotoxicity</td>
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<td>Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts. (…)</td>
</tr>
</tbody>
</table>

5.10 Hemorrhage
Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Iclusig in the phase 2 trial with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% (4/449) and 4/449, respectively. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia [see Warnings and Precautions (5.13)]. Intermittent Iclusig for serious or severe hemorrhage and evaluate [see Dosage and Administration (2.3)].

5.13 Myelosuppression
Myelosuppression was reported as an adverse reaction in 59% (266/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Iclusig. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (…) |

5.14 Tumor Lysis Syndrome
Two patients (1%) treated with Iclusig developed serious tumor lysis syndrome. One case occurred in a patient with advanced AP-CML and one case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig.

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Previously Treated CML or Ph+ ALL
The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. (…) At the time of analysis (48 months of follow-up), 133 patients (30%) were ongoing (110 CP-CML; 20 AP-CML; 3 BP-CML; 0 Ph+ ALL), and the median duration of treatment with Iclusig was 22.2 months in patients with CP-CML; 19.4 months in patients with AP-CML; 2.9 months in patients with BP-CML, and 2.7 months in patients with Ph+ ALL. (…) The rates of treatment-emergent adverse reactions resulting in discontinuation were 19% in CP-CML, 12% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse reactions that led to treatment discontinuation was thrombocytopenia (4%). (See Table 5) (…)

Laboratory Abnormalities
(…) Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (See Table 7) (…)

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use
One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (40%) as compared with patients < 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a similar hematologic response rate (45%) as compared with patients < 65 years of age (44%). (…) |

14 CLINICAL STUDIES
The safety and efficacy of Iclusig in patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter trial. Efficacy results described below should be interpreted within the context of updated safety information [see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1, 5.2)]. All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML], accelerated phase CML [AP-CML], or blast phase CML [BP-CML] or Ph+ ALL), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation. Resistance in CP-CML, while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response by 3 months, a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML; by 1 month in BP-CML and Ph+ ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ ALL.

The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). The trial enrolled 449 patients, of which 444 were eligible for efficacy analysis: 267 patients with CP-CML (R/I Cohort: n=203, T315I: n=64), 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ ALL. Five patients were not eligible for efficacy analysis due to lack of confirmation of T315I mutation status, and these patients had not received prior dasatinib or nilotinib. (See Table 11) (…) |

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1 INDICATIONS AND USAGE

1.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.2 RET-Mutant Medullary Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.3 RET Fusion-Positive Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection
Select patients for treatment with GAVRETO based on the presence of a RET gene fusion (NSCLC or thyroid cancer) or RET gene mutation (MTC) [see Clinical Pharmacology (12.3), Clinical Studies (14)]. Information on FDA-approved tests for RET gene fusion (NSCLC) is available at http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of RET gene fusion (thyroid cancer) and RET gene mutations is not currently available.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET altered solid tumors in ARROW [see Clinical Studies (14)]. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

RET Fusion-Positive Non-Small Cell Lung Cancer
The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW [see Clinical Studies (14)]. (…)Table 4 summarizes the adverse reactions in RET Fusion-Positive NSCLC Patients in ARROW.

RET-altered Thyroid Cancer
The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW [see Clinical Studies (14.2, 14.3)]. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year. (…) Table 6 summarizes the adverse reactions occurring in RET-altered Thyroid Cancer Patients in ARROW.

Table 7 summarizes the laboratory abnormalities occurring in RET-altered Thyroid Cancer Patients in ARROW.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use
The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for RET-mutant MTC and RET-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of RET-mutant MTC and RET-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)].

The safety and effectiveness of GAVRETO have not been established in pediatric patients with RET-fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET-mutant MTC or RET-fusion thyroid cancer.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics
Pralsetinib exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.

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<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.9 Metabolic Status (In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.)</td>
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The Qτ interval prolongation potential of GAVRETO was assessed in 34 patients with RET fusion-positive solid tumors administered at the recommended dosage. No large mean increase in QTc (> 20 ms) was detected in the study.

14 CLINICAL STUDIES
14.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
The efficacy of GAVRETO was evaluated in patients with RET fusion-positive metastatic NSCLC in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). The study enrolled, in separate cohorts, patients with metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Identification of a RET gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. Among the 134 patients in the efficacy population(s) described in this section, samples from 59% of patients were retrospectively tested with the Life Technologies Corporation Oncomine Dx Target Test (ODxTT). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. Patients received GAVRETO 400mg orally once daily until disease progression or unacceptable toxicity.

Metastatic RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy
Efficacy was evaluated in 87 patients with RET fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy enrolled into a cohort of ARROW. The median age was 60 years (range: 28 to 85); 49% were female, 53% were White, 35% were Asian, 6% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%), 59% of patients had metastatic disease, and 43% had neither history of or current CNS metastasis. Patients received a median of 2 prior systemic therapies (range 1-6); 45% had prior anti-PD-1/PD-L1 therapy and 25% had prior kinase inhibitors. A total of 52% of the patients received prior radiation therapy. RET fusions were detected in 77% of patients using NGS (45% tumor samples; 26% blood or plasma samples, 6% unknown), 21% using FISH, and 2% using other methods. The most common RET fusion partners were KIF5B (75%) and CCDC6 (17%). Efficacy results for RET fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarized in Table 8.

For the 39 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 59% (95% CI: 42, 74) and the median DOR was not reached (95% CI: 11.3, NE). Among the 87 patients with RET-fusion positive NSCLC, 8 had measurable CNS metastases at baseline as assessed by BICR. No patients received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 8 patients including 2 patients with a CNS complete response; 75% of responders had a DOR of ≥ 6 months.

Treatment-naive RET Fusion-Positive NSCLC
Efficacy was evaluated in 27 patients with treatment-naive RET fusion-positive NSCLC with measurable disease enrolled into ARROW. The median age was 65 years (range 30 to 97); 52% were female, 59% were White, 33% were Asian, and 4% were Hispanic or Latino. ECOG performance status was 0-1 for 96% of the patients and all patients (100%) had metastatic disease. 37% had either history of or current CNS metastasis. RET fusions were detected in 67% of patients using NGS (41% tumor samples; 32% blood or plasma samples, 6% unknown) and 33% using FISH. The most common RET fusion partners were KIF5B (70%) and CCDC6 (11%). Efficacy results for treatment-naïve RET fusion-positive NSCLC are summarized in Table 9.

14.2 RET-Mutant Medullary Thyroid Cancer
The efficacy of GAVRETO was evaluated in patients with RET-mutant MTC in a multicenter, open-label, multi-cohort clinical trial (ARROW; NCT03037385). RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib
Efficacy was evaluated in 55 patients with RET-mutant metastatic MTC previously treated with cabozantinib or vandetanib (or both). The median age was 59 years (range: 25 to 83); 78% were male, 76% were White, 5% were Asian, 5% were Hispanic/Latino, ECOG performance status was 0-1 (95%) or 2 (5%), and 7% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-7). RET mutation status was detected in 73% using NGS (55% tumor sample, 18% plasma), 26% using PCR sequencing, and 2% other. The primary mutations used to identify and enroll patients are described in Table 10. Efficacy results for RET-mutant MTC previously treated with cabozantinib or vandetanib are described in Table 9.

14.4 RET Fusion-Positive Thyroid Cancer
The efficacy of GAVRETO was evaluated in RET fusion-positive metastatic thyroid cancer patients in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). All patients with RET fusion-positive thyroid cancer were required to have disease progression following standard therapy, measurable disease by RECIST version 1.1, and have RET fusion status as detected by local laboratories. 98% had metastatic disease, and 78% had either history of or current CNS metastases. Twenty-eight percent (28%) had received 3 lines of prior systemic therapy (including 10% PD-1/PD-L1 inhibitors, 10% radioactive iodine, 34% kinase inhibitors). RET mutation status was detected in 90% using NGS (52% tumor sample, 35% plasma, 34% blood) and 10% using PCR sequencing. The primary mutations used to identify and enroll patients are described in Table 10. Efficacy results for RET Fusion-Positive Thyroid Cancer are summarized in Table 12.
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| 022307, 03/28/2019                     | Prasugrel (2) | Cardiology | CYP2C9 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 8 USE IN SPECIFIC POPULATIONS 8.9 Metabolic Status
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. |
| 022307, 03/28/2019                     | Prasugrel (3) | Cardiology | CYP3A5 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 8 USE IN SPECIFIC POPULATIONS 8.9 Metabolic Status
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. |
| 022307, 03/28/2019                     | Prasugrel (4) | Cardiology | CYP2B6 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 8 USE IN SPECIFIC POPULATIONS 8.9 Metabolic Status
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. |
| 008316, 06/22/2017                     | Primaquine (1) | Infectious Diseases | G6PD | Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage | CONTRAINDICATIONS
Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings).

WARNINGS
Hemolytic anemia and G6PD deficiency
Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adverse medical support and follow-up to manage hemolytic risk should be available. Primaquine should not be prescribed for patients with severe G6PD deficiency (see Contraindications). |

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<th>Biomarker</th>
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<th>Labeling Text</th>
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</thead>
</table>
| 008316, 06/22/2017                      | Primaquine (2) | Infectious Diseases | CYB5R | Precautions, Adverse Reactions | PRECAUTIONS Blood Monitoring

Since anaemia, methemoglobinemia, and leukopenia have been observed following administration of large doses of primaquine, the adult dosage of 1 tablet (≈ 15 mg base) daily for fourteen days should not be exceeded. In G6PD normal patients it is also advisable to perform routine blood examinations (particularly blood cell counts and hemoglobin determinations) during therapy.

ADVERSE REACTIONS

Hematologic

Leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.

OVERDOSAGE

Symptoms of overdosage of primaquine phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia, and anemia. The most striking symptoms are granulocytopenia and acute hemolytic anemia in G6PD deficient patients. Acute hemolysis occurs, but patients recover completely if the dosage is discontinued.

<table>
<thead>
<tr>
<th>007898</th>
<th>Probenecid</th>
<th>Rheumatology</th>
<th>G6PD</th>
<th>Adverse Reactions</th>
<th>Labeling not electronically available on Drugs@FDA</th>
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<tbody>
<tr>
<td>020545</td>
<td>Procainamide</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>Adverse Reactions, Clinical Pharmacology</td>
<td>Labeling not electronically available on Drugs@FDA</td>
</tr>
</tbody>
</table>
| 021416, 11/02/2018                      | Propafenone | Cardiology | CYP2D6 | Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION

(…) The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor [see Warnings and Precautions (5.4) and Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS

5.4 Drug Interactions: Simultaneous Use with Inhibitors of Cytochrome P450 Isoenzymes 2D6 and 3A4

Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6 activity and to a somewhat lesser extent in other demographic groups. Drugs that inhibit these CYP pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP2D6; ketoconazole, erythromycin, saquinavir, and grapefruit juice for CYP3A4; and amiodarone and tobacco smoke for CYP1A2) can be expected to cause increased plasma levels of propafenone.

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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>021438, 11/19/2013</td>
<td>Propranolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.</td>
</tr>
<tr>
<td>073644, 07/17/2014</td>
<td>Protriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>Drugs Metabolized by Cytochrome P450 2D6</td>
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<tr>
<td>089338, 02/02/2010</td>
<td>Quinidine</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>(…) Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient “poor metabolizers” from the majority-phenotype “extensive metabolizers.” When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the case of produgs whose actions are actually mediated by P450IID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antifluvial effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers. Quinidine is not metabolized by cytochrome P450IID6, but therapeutic levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6. (…)</td>
</tr>
</tbody>
</table>

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<td>021799, 06/19/2019</td>
<td>Quinine Sulfate (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.3 Hemolytic Anemia</td>
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<td>Acute hemolytic anemia has been reported in patients receiving quinine for treatment of malaria, including patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The cause for the acute hemolytic anemia in quinine-treated patients with malaria and its potential relationship with G6PD deficiency has not been determined. Closely monitor hemoglobin and hematocrit during quinine treatment. Quinine should be discontinued if patients develop acute hemolytic anemia.</td>
</tr>
<tr>
<td>021799, 06/19/2019</td>
<td>Quinine Sulfate (2)</td>
<td>Infectious Diseases</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS</td>
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<td>7.2 Effects of Quinine on the Pharmacokinetics of Other Drugs</td>
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<td>Desipramine (CYP2D6 substrate) Quinine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. (…)</td>
</tr>
<tr>
<td>216993, 07/20/2023</td>
<td>Quizartinib</td>
<td>Oncology</td>
<td>FLT3</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>VANFLYTA is indicated in combination with standard cytoreductive and anthracycline induction and cytoreductive consolidation, and as maintenance chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test [see Dosage and Administration (2.1) and Clinical Studies (14)].</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection Select patients for the treatment of AML with VANFLYTA based on the presence of FLT3-ITD mutation positivity [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of FLT3-ITD mutation in AML is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 QT Prolongation, Torsades de Pointes, and Cardiac Arrest (…) Of the 265 patients with newly diagnosed FLT3-ITD-positive AML treated with VANFLYTA in combination with chemotherapy in the clinical trial, 2.3% found to have a QTcF greater than 500 ms and 10% of patients had an increase from baseline QTcF greater than 60 ms. (…)</td>
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<td></td>
<td>6 ADVERSE REACTIONS</td>
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<td>Neutropenic FLT3-ITD positive AML The safety of VANFLYTA (35.4 mg orally once daily with chemotherapy, 26.5 mg to 53 mg orally once daily as maintenance) in adult patients with newly diagnosed FLT3-ITD positive AML is based on QuANTUM-First, a randomized, double-blind clinical trial of VANFLYTA (n=265) or placebo (n=268) with chemotherapy (see Clinical Studies (14)). (See Tables 5 and 6) (…) Other Clinical Trials Clinically relevant adverse reactions in &lt;10% of patients who received quizartinib for relapsed or refractory FLT3-ITD positive AML, an indication for which VANFLYTA is not approved, included differentiation syndrome (5%) and acute febrile neutrophilic dermatosis (3%).</td>
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<td></td>
<td>14 CLINICAL STUDIES</td>
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<td>The efficacy of VANFLYTA in combination with chemotherapy was evaluated in QuANTUM-First (NCT02686653), a randomized, double-blind, placebo-controlled study of 539 patients with newly diagnosed FLT3-ITD positive AML. FLT3-ITD status was determined prospectively with a clinical trial assay and verified retrospectively using the companion diagnostic LeukoStrat® CDx FLT3 Mutation Assay, which is an FDA-approved test for selection of patients with AML for VANFLYTA treatment. (…) The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Of the 539 randomized patients, the median age was 56 years (range 20-75 years); 46% were male; 60% were White; 29% were Asian, 1% were Black or African American, and 10% were other races. Eighty-four percent had an Eastern Cooperative Oncology Group (ECOG) baseline performance status of 0 or 1. The majority of the patients (72%) had intermediate risk cytogenetics at baseline. FLT3-ITD variant allelic frequency (VAF) was 3-25% in 30% of patients, &gt;25-50% in 52% of patients, and &gt;50% in 12% of patients. NPM1 mutations were identified in 52% of patients.</td>
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<tr>
<td>020973, 06/07/2018</td>
<td>Rabeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
</tr>
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<td>Tacrolimus Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics Metabolism (…) CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug. Drug Interaction Studies Combined Administration with Antimicrobials Sixteen healthy subjects genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg ACIPHEX delayedrelease tablets, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. (…)</td>
</tr>
</tbody>
</table>

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<tr>
<td>020815, 06/27/2018</td>
<td>Ramucirumab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>1 INDICATIONS AND USAGE</td>
<td>12.5 Pharmacogenomics – Cyramza in combination with erlotinib, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. CYRAMZA, in combination with docetaxel, is indicated for patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.</td>
</tr>
<tr>
<td>022145, 03/05/2018</td>
<td>Raltegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.5 Pharmacogenomics – UGT1A1 Polymorphism</td>
</tr>
<tr>
<td>125477, 05/28/2020</td>
<td>Clopidogrel</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>14 CLINICAL STUDIES</td>
<td>12.5 Pharmacogenomics – In a clinical study in evaluating ACIPHEX delayed-release tablets in Japanese adult patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. The clinical relevance of this is not known. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.</td>
</tr>
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### 6.1 Clinical Trials Experience

**Non-Small Cell Lung Cancer**

CYRAMZA Administered in Combination with Erlotinib (RELAY)

The safety of CYRAMZA was evaluated in RELAY (see Clinical Studies (14.2)). Patients who had previously untreated EGFR exon 19 deletion or exon 21 (L858R) substitution mutation-positive metastatic NSCLC. (…)

### 14 CLINICAL STUDIES

**14.2 Non-Small Cell Lung Cancer**

RELAY

The efficacy of CYRAMZA in combination with erlotinib was evaluated in RELAY (NCT02411448), a multinational, randomized, double-blind, placebo-controlled, multicenter study in patients with previously untreated metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutation. Patients in RELAY were required to have measurable disease, ECOG PS of 0 or 1, no central nervous system (CNS) metastases, and no known EGFR T790M mutations at baseline. Patients were randomized (1:1) to receive either CYRAMZA 10 mg/kg or placebo every 2 weeks as an intravenous infusion, in combination with erlotinib 150 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (East Asia versus other), gender, EGFR mutation (exon 19 deletion versus exon 21 [L858R] substitution mutation), and local EGFR testing method (therascere screen® and cobas® versus other polymerase chain reaction [PCR] and sequencing-based methods).

A total of 449 patients were randomized, 224 to the CYRAMZA-treatment group and 225 to the placebo-treatment group. Baseline demographics and disease characteristics were similar between treatment arms. The median age was 65 years (range 23-89); 63% of patients were female; 77% were Asian and 22% were White; 52% had ECOG PS 0; 61% were never smokers; 54% had exon 19 mutation deletions, and 45% had exon 21 (L858R) substitution mutations. (…)

**REVEL**

(…) Tumor EGFR status was unknown for the majority of patients (65%). Where tumor EGFR status was known (n=445), 7.4% were positive for EGFR mutation (n=33). No data were collected regarding tumor ALK rearrangement status. (…)

<table>
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<th>Oncology</th>
<th>RAS</th>
<th>Clinical Studies</th>
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</table>

### 6.3 Colorectal Cancer

(…) Randomization was stratified by geographic region, tumor KRAS status, and time to disease progression after beginning first-line treatment (<6 months versus ≥6 months).

Demographic and baseline characteristics were similar between treatment arms. Median age was 62 years (range 30-85); 57% of patients were female; 57% were Asian and 20% of patients were White; 76% had ECOG PS 0; 49% of patients had KRAS mutant tumors; and 24% of patients had <6 months from time to disease progression after beginning first-line treatment. (…)

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<tr>
<th>103946, 12/12/2019</th>
<th>Rasburicase (1)</th>
<th>Oncology</th>
<th>G6PD</th>
<th>BOXED WARNING</th>
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#### BOXED WARNING

**WARNING:** HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

Hemolysis

Do not administer Elitek to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Elitek if hemolysis occurs. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek therapy (4, 5.2).

### 4 CONTRAINDICATIONS

Elitek is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) [see Boxed Warning, Warnings and Precautions (5.2)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.2 Hemolysis

Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in ≤1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Boxed Warning, Contraindications (4)].

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<tr>
<th>103946, 12/12/2019</th>
<th>Rasburicase (2)</th>
<th>Oncology</th>
<th>CYBSR</th>
<th>BOXED WARNING</th>
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#### BOXED WARNING

**WARNING:** HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

Methemoglobinemia

Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek if methemoglobinemia occurs (4, 5.3).

### 4 CONTRAINDICATIONS

Elitek is contraindicated in patients with a history of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase [see Boxed Warning, Warnings and Precautions (5)].

### 5 WARNINGS AND PRECAUTIONS

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<td>761108, 04/27/2022</td>
<td>Ravulizumab-cwvz</td>
<td>Neurology</td>
<td>ACHR</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1.3 Generalized Myasthenia Gravis (gMG) is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (ACHR) antibody-positive.</td>
</tr>
<tr>
<td>203085, 02/13/2020</td>
<td>Regorafenib</td>
<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1.1 Colorectal Cancer (CRC) STIVARGA is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wildtype, an anti-EGFR therapy.</td>
</tr>
<tr>
<td>218213, 11/15/2023</td>
<td>Repotrectinib</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1.1 Indications and Usage AUGTYRO is indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) [see Dosage and Administration (2.1)].</td>
</tr>
</tbody>
</table>

**5.3 Methemoglobinemia**

In clinical studies, methemoglobinemia occurred in <1% patients receiving Elitek. These included cases of serious hypoxemia requiring intervention with medical support measures. It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia. Immediately and permanently discontinue Elitek administration in any patient identified as having developed methemoglobinemia. Institute appropriate monitoring and support measures (e.g., transfusion support, methylene-blue administration) [see Boxed Warning, Contraindications (4)].

**6.3 Generalized Myasthenia Gravis (gMG)**

ULTOMIRIS is indicated for the treatment of adult patients with gMG who are anti-AChR antibody-positive. Patients with gMG with a positive serologic test for anti-AChR antibodies, Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, and Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥6 were enrolled.

**14.1 Colorectal Cancer**

The primary sites of disease were colon (65%), rectum (29%), or both (6%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutations. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutation/neutral mutations received panitumumab or cetuximab.

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 209092, 01/21/2020 | Ribociclib (1) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Studies | KISQALI is indicated in combination with:  
  - an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or  
  - fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy. | 1 INDICATIONS AND USAGE |
|          |                       |               |                   |            |                   |                |
| 209092, 01/21/2020 | Ribociclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | KISQALI is indicated in combination with:  
  - an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or  
  - fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy. | 1 INDICATIONS AND USAGE |

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<tr>
<td>212728, 02/27/2020</td>
<td>Rimegepant</td>
<td>Anesthesiology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy. The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. (…)</td>
</tr>
<tr>
<td>213535, 08/07/2020</td>
<td>Radipant</td>
<td>Neurology</td>
<td>SMN1, SMN2</td>
<td>Clinical Studies</td>
<td>(…) The median age of onset of clinical signs and symptoms of Type 1 SMA in patients enrolled in Part 1 of Study 1 was 4.0 months (range: 2.0 to 5.8). All patients had genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies. (…)</td>
</tr>
<tr>
<td>020272, 01/25/2019</td>
<td>Risperidone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Absorption Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=±25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=±10%) when compared to a solution. Pharmacokinetic studies showed that RISPERDAL M-TAB Oral Disintegrating Tablets and RISPERDAL Oral Solution are bioequivalent to RISPERDAL Tablets. Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5–6 days (measured in extensive metabolizers). Metabolism (…) CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are “poor metabolizers”) and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert rimegepant rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers. Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of rimegepant to 9-hydroxyrisperidone (see Drug Interactions (7)). This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given RISPERDAL do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL may cause a decrease in the combined plasma</td>
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<td>215830, 06/23/2023</td>
<td>Ritlecitinib</td>
<td>Oncology</td>
<td>XXX</td>
<td>GST</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>103705, 12/17/2021</td>
<td>Rituximab</td>
<td>Oncology</td>
<td>MS4A1 (CD20 antigen)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
</tbody>
</table>

1.1 Non-Hodgkin’s Lymphoma (NHL)

- Rituxan (rituximab) is indicated for the treatment of patients with:
  - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy regimen.
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

1.2 Chronic Lymphocytic Leukemia (CLL)

- Rituxan (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dose for Non-Hodgkin’s Lymphoma (NHL)

- The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:
  - Relapsed or refractory, low-grade or follicular, CD20-Positive, B-Cell NHL: administer once weekly for 4 or 8 doses.
  - Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL: administer once weekly for 4 doses.
  - Previously Untreated, Follicular, CD20-Positive, B-Cell NHL: administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance therapy every 6 months and for a maximum of 16 doses.
  - Diffuse Large B-Cell NHL: follow completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience in Lymphoid Malignancies

5.1 Cytopenias and hypogammaglobulinemia

- Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [See Clinical Studies (14.1)]. Most patients received Rituxan 375 mg/m² weekly for 4 doses.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- Rituxan is not indicated for the treatment of pediatric patients (6 months and older) with B-cell acute leukemia (B-AL) in combination with chemotherapy.

- Rituxan is not indicated as single-agent maintenance therapy in pediatric patients aged 6 months and older, with: Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy regimen.

- Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

- Diffuse Large B-Cell NHL

- Administer on Day 1 of each cycle of chemotherapy, for up to 8 infusions.

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<tr>
<td>021366, 11/02/2018</td>
<td>Ropivacaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>Methemoglobinemia. Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6- phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…).</td>
</tr>
<tr>
<td>020533, 11/02/2018</td>
<td>Ropivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>Methemoglobinemia. Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6- phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…).</td>
</tr>
<tr>
<td>021366, 11/09/2018</td>
<td>Rosuvastatin</td>
<td>Endocrinology</td>
<td>SLCO1B1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMAKOLOGY 12.5 Pharmacogenomics Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1.</td>
</tr>
</tbody>
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| 761286, 06/20/2023                     | Rozanolixizumab-noli (1) | Neurology | ACHR       | Indications and Usage, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
RYSTIGGO is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive. |
| 761286, 06/20/2023                     | Rozanolixizumab-noli (2) | Neurology | MUSK       | Indications and Usage, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
RYSTIGGO is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive. |
| 209115, 06/10/2022                     | Rubraca (1) | Oncology | BRCA       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Metastatic Castration-Resistant Prostate Cancer with BRCA Mutations
Rubraca is indicated for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic) associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on objective response rate and duration of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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(SLC01B1 521T > C). The frequency of this genotype (i.e., SLC01B1 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established.

In Study 1 [see Clinical Studies (14)], the pharmacological effect of rozanolixizumab-noli was assessed by measuring the decrease in serum IgG levels and AChR and MuSK autoantibody levels. In patients testing positive for AChR and MuSK autoantibodies who were treated with RYSTIGGO, there was a reduction in total IgG levels relative to baseline. Decreases in AChR autoantibody and MuSK autoantibody levels followed a similar pattern.

The efficacy of RYSTIGGO for the treatment of generalized myasthenia gravis (gMG) in adults who are anti-AChR antibody positive or anti-MuSK antibody positive was established in a multicenter, randomized, double-blind, placebo-controlled study (Study 1; NCT03971422). The study included a 4-week screening period and a 6-week treatment period followed by 8 weeks of observation. During the treatment period, RYSTIGGO or placebo were administered subcutaneously once a week for six weeks. Study 1 enrolled patients who met the following criteria:

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<tbody>
<tr>
<td><strong>Table 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Select patients for the treatment of mCRPC with Rubraca based on the presence of a deleterious BRCA mutation (germline and/or somatic) in plasma specimens [see Clinical Studies (14.2)]. A negative result from a plasma specimen does not mean that the patient’s tumor is negative for BRCA mutations. Should the plasma specimen have a negative result, consider performing further testing using tumor specimens as clinically indicated. Information on the FDA-approved tests for the detection of a BRCA mutation in patients with ovarian cancer or with prostate cancer is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
</tr>
<tr>
<td><strong>Table 5</strong></td>
<td></td>
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#### 6 ADVERSE REACTIONS

**6.1 Clinical Trials Experience**

**Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy**

The safety of Rubraca 600 mg twice daily was evaluated in a single arm trial (TRITON2) [see Clinical Studies (14.2)]. TRITON2 enrolled 209 patients with HRD-positive mCRPC, including 115 with BRCA-mutated mCRPC. Among the patients with BRCA-mutated mCRPC, the median duration of Rubraca treatment was 6.5 months (range 0.5 to 26.7) (…)

| Tables 4 and 5 summarize the adverse reactions and laboratory abnormalities, respectively, in patients with BRCA-mutated mCRPC in TRITON2. (See Tables 4 and 5) (…) |

#### 14 CLINICAL STUDIES

**14.1 Ovarian Cancer**

**Maintenance Treatment of Recurrent Ovarian Cancer**

(…) Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564), and the FoundationFocus™ CDx BRCA LOH test (n=518). Of the samples evaluated with both tests, homologous recombination deficiency (HRD) positive status (as defined by the presence of a deleterious BRCA mutation or high genomic loss of heterozygosity) was confirmed by the FoundationFocus™ CDx BRCA LOH test for 94% (313/332) of HRD-positive patients determined by the CTA; and of these, tumor BRCA (tBRCA) mutant status was confirmed by the FoundationFocus™ CDx BRCA LOH test for 96% (177/178) of tBRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the tBRCA patients had a germline BRCA mutation and 30% (56/186) had a somatic BRCA mutation. ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rubraca as compared with placebo in all patients, and in the HRD and tBRCA subgroups. Results from a blinded independent radiology review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (with 22% of events). (See Table 6, Figures 1, 2, and 3)

| 14.2 Metastatic Castration-Resistant Prostate Cancer with BRCA mutations |

The efficacy of Rubraca was investigated in TRITON2 (NCT02952534), an ongoing multi-center, single arm clinical trial in patients with BRCA-mutated mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. There were 115 patients with either germline or somatic BRCA mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline by independent radiology review (IRR). (…)

| All 62 patients had a deleterious somatic or germline BRCA mutation detected from either central plasma (26%), central tissue (32%), or local (42%) testing. Of the 62 patients, 60% had a somatic BRCA mutation, 34% had a germline BRCA mutation, and 15% had a BRCA1 mutation. The major efficacy outcomes of the study were confirmed ORR by IRR using modified RECIST v1.1/PCWG3 criteria and DOR. Efficacy results of TRITON2 are provided in Table 7. The ORR by IRR was similar in patients with germline versus somatic BRCA mutation. (See Table 7) |

| **Table 6**                                           | 12 CLINICAL PHARMACOLOGY |
|                                                     | 12.3 Pharmacokinetics    |
|                                                     | Specific Populations     |
|                                                     | CYP Enzyme Polymorphism  |
| Rucaparib (2)                                        | 2019/11/5, 08/2020      |
| Oncology                                             | CYP2D6                   |
| Clinical Pharmacology                                 | 12.3.1 Pharmacokinetics  |
|                                                      | Specific Populations     |
|                                                      | CYP Enzyme Polymorphism  |
|                                                      | Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups. |
| **Table 7**                                           | 12 CLINICAL PHARMACOLOGY |
|                                                     | 12.3 Pharmacokinetics    |
|                                                     | Specific Populations     |
|                                                     | CYP Enzyme Polymorphism  |
| Rucaparib (3)                                        | 2019/11/5, 05/2020      |
| Oncology                                             | CYP1A2                   |
| Clinical Pharmacology                                 | 12.3.1 Pharmacokinetics  |
|                                                      | Specific Populations     |
|                                                      | CYP Enzyme Polymorphism  |
|                                                      | Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups. |
| **Table 8**                                           | 5 WARNINGS AND PRECAUTIONS |
|                                                     | 5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia |
|                                                     | Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur in patients treated with Rubraca, and are potentially fatal adverse reactions. In 1146 treated patients [see Adverse Reactions (6.1)], MDS/AML occurred in 20 patients (1.7%), including those in long term follow-up. Of these, 8 occurred during treatment or during the 28 day safety follow-up (0.7%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 53 months. The cases were typical of secondary MDS/cancer-therapy-related AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or DNA damaging agents. In TRITON2, MDS/AML was not observed in patients with mCRPC (n=209) regardless of homologous recombination deficiency (HRD) mutation [see Adverse Reactions (6.1)]. |
| **Table 9**                                           | 6 ADVERSE REACTIONS      |
|                                                     | 6.1 Clinical Trials Experience |

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<td>761115, 02/03/2023</td>
<td>Sacituzumab Govitecan-hziy (1)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
<td>Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy. The safety of Rubraca 600 mg twice daily was evaluated in a single arm trial (TRITON2) [see Clinical Studies (14.2)]. TRITON2 enrolled 209 patients with HRD-positive mCRPC, including 115 with BRCA-mutated mCRPC. Among the patients with BRCA-mutated mCRPC, the median duration of Rubraca treatment was 6.5 months (range 0.5 to 26.7). (...)</td>
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<td>761115, 02/03/2023</td>
<td>Sacituzumab Govitecan-hziy (2)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>Sacituzumab Govitecan-hziy (3)</td>
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<td>ESR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1. INDICATIONS AND USAGE</td>
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<td></td>
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<td></td>
<td>1.2 Locally Advanced or Metastatic Breast Cancer</td>
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<td>• TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.</td>
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<td>• TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.</td>
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<td></td>
<td>6 ADVERSE REACTIONS</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>6.1 Clinical Trials Experience</td>
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<td>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY in 1063 patients from four studies, JMMU-132-01, ASCENT, TROPICS-02, and TROPHY which included 366 patients with mTNBC, 322 patients with hormone receptor-positive (HR+)+human epidermal growth factor receptor 2-negative (HER2-) breast cancer, and 180 patients with mUC. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses of 10 mg/kg until disease progression or unacceptable toxicity. (…)</td>
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<td></td>
<td>Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer TROPICS-02 Study</td>
</tr>
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<td>The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label, study (TROPICS-02) in patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression occurred within 12 months). (See Tables 6 and 7) (…)</td>
</tr>
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6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY in 1063 patients from four studies, JMMU-132-01, ASCENT, TROPICS-02, and TROPHY which included 366 patients with mTNBC, 322 patients with hormone receptor-positive (HR+)+human epidermal growth factor receptor 2-negative (HER2-) breast cancer, and 180 patients with mUC. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses of 10 mg/kg until disease progression or unacceptable toxicity. (…) Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer TROPICS-02 Study
The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label, study (TROPICS-02) in patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression occurred within 12 months). (See Tables 6 and 7) (…)
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8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Of the 366 patients with TNBC who were treated with TRODELVY, 19% of patients were 65 years and 3% were 75 years and older. No overall differences in safety and effectiveness were observed between patients ≥ 65 years of age and younger patients. Of the 322 patients with HR+HER2- breast cancer who were treated with TRODELVY, 26% of patients were 65 years and older and 6% were 75 years and older. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%). Of the 180 patients with UC who were treated with TRODELVY, 59% of patients were 65 years and older and 27% were 75 years and older. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (8%).

14 CLINICAL STUDIES

14.2 Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer

The efficacy of TRODELVY was evaluated in a multicenter, open label, randomized study (TROPICS-02: NCT03901339) conducted in 543 patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+ or IHC 3−) breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if recurrence occurred within 12 months). (…)

<table>
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<tr>
<th>020772, 05/25/2022</th>
<th>Sacrosidase</th>
<th>Inborn Errors of Metabolism</th>
<th>Nonspecific (Congenital Sucrase-Isomaltase Deficiency)</th>
<th>Indications and Usage, Adverse Reactions, Clinical Pharmacology</th>
<th>INDICATIONS AND USAGE Splenial (sacrosidase) Oral Solution is indicated as oral replacement therapy of the genetically determined sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID).</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1 INDICATIONS AND USAGE ENSPRYNG is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.</td>
</tr>
<tr>
<td>761149, 08/14/2020</td>
<td>Satralizumab-imege</td>
<td>Neurology</td>
<td>AQP4</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience The safety of ENSPRYNG was evaluated in two randomized, placebo-controlled clinical trials (Study 1 evaluated ENSPRYNG without concurrent immunosuppressive therapy (IST) and Study 2 evaluated ENSPRYNG with concurrent IST), which included 41 anti-AQP4 seropositive patients treated with ENSPRYNG in Study 1 and 26 anti-AQP4 seropositive patients treated with ENSPRYNG in Study 2 [see Clinical Studies (14)]. In the double-blind, controlled trials, the median exposure time on ENSPRYNG treatment was approximately 2 years in Study 1 and approximately 3 years in Study 2. The median exposure time on placebo treatment was approximately 1 year in both Study 1 and Study 2. (…)</td>
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</table>
| 213246, 09/21/2022                     | Selpercatinib | Oncology | RET | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | **1 INDICATIONS AND USAGE**

1.1 RET Fusion-Positive Non-Small Cell Lung Cancer

RETevmo is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test.

1.2 RET-Mutant Medullary Thyroid Cancer

RETevmo is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy.

1.3 RET Fusion-Positive Thyroid Cancer

RETevmo is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

1.4 Other RET Fusion-Positive Solid Tumors

RETevmo is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic therapy and/or have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with RETevmo based on the presence of a RET gene fusion (NSCLC, thyroid cancer, or other solid tumors) or specific RET gene mutation (MTC) in tumor specimens [see Clinical Studies (14.3)]. Information on FDA-approved test(s) for the detection of RET gene fusions and RET gene mutations is available at: http://www.fda.gov/CompanionDiagnostics.

An FDA-approved companion diagnostic test for the detection of RET gene fusions and RET gene mutations in plasma or in tumors other than NSCLC and thyroid cancer is not currently available.

3 ADVERSE REACTIONS

3.1 General Adverse Reactions

The most common (incidence ≥ 25%) and serious adverse reactions observed in RETevmo-treated patients in studies (LIBRETTO-001, NCT03157128) were increased AST/ALT (43%), increased creatinine (33%), and increased amylase (28%).

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

4 USE IN SPECIFIC POPULATIONS

4.1 Pregnancy

The efficacy and safety of RETevmo have been evaluated in pregnant women and in nursing mothers. There is no evidence of fetal harm. The decision to administer RETevmo to pregnant women should be made considering the benefit-risk assessment for each individual patient.

4.2 Nursing Mothers

It is unknown if RETevmo is excreted in human milk. The decision to administer RETevmo to a nursing mother should be made considering the benefit-risk assessment for each individual patient.

4.3 Pediatric Use

The safety and effectiveness of RETevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate).

Use of RETevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older (see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)). The safety and effectiveness of RETevmo have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETevmo have not been established in pediatric patients for other indications (see Indications and Usage (1)).

5 CLINICAL STUDIES

5.1 RET Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of RETevmo was evaluated in patients with advanced RET fusion-positive NSCLC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with advanced or metastatic NSCLC without prior systemic therapy in separate cohorts. Identification of a RET gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH). Adult patients received RETevmo 160 mg orally twice daily until unacceptable toxicity or disease progression. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

The efficacy of RETevmo in patients with RET fusion-positive NSCLC previously treated with platinum chemotherapy was evaluated in 105 patients with RET fusion-positive NSCLC previously treated with platinum chemotherapy enrolled in a cohort of LIBRETTO-001.
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<td>Sevoflurane</td>
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<td>Anesthesiology</td>
<td>CACNA1S, RYR1 (Genetic Susceptibility to)</td>
<td>02/04/78, 11/01/2022</td>
<td><strong>CONTRAINDICATIONS</strong></td>
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<td>213793, 06/16/2022</td>
<td>Setmelanotide (1)</td>
<td>Endocrinology</td>
<td>LEPR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to: • Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) [see Dosage and Administration (2.1)]. • Bardet-Biedl syndrome (BBS) [see Dosage and Administration (2.2)]. Limitations of Use: IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective: • Obesity due to suspected POMC, PCSK1, or LEPR deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign. • Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.</td>
</tr>
</tbody>
</table>

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection - POMC, PCSK1, or LEPR Deficiency

• Select patients for treatment with IMCIVREE who have genetically determined or suspected deficiency of POMC, PCSK1, or LEPR [see Clinical Studies (14)]. • Treat patients with variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) in the clinical context of the patient [see Clinical Studies (14)]. • Information on an FDA-approved test for the detection of variants in the POMC, PCSK1, or LEPR is available at http://www.fda.gov/CompanionDiagnostics. |

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of IMCIVREE was evaluated in two 52-week, open-label clinical studies of 27 patients with obesity due to POMC, PCSK1, or LEPR deficiency with IMCIVREE, and 39% screened negative. The 61% of patients who screened positive for antibodies to IMCIVREE were inconclusive for antibodies to IMCIVREE in the confirmatory assay. There was no observation of a rapid decline in IMCIVREE concentrations to suggest the presence of anti-drug antibodies. (…) Approximately 13% of adult and pediatric patients with LEPR-deficiency (3 patients) confirmed positive for antibodies to alpha-MSH that were classified as low-titer and non-persistent. Of these 3 patients (13%), 2 tested positive post-IMCIVREE treatment and 1 was positive pretreatment. None of the patients with POMC-deficiency were confirmed to have antibodies to alpha-MSH. (…) |

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of IMCIVREE have been established for chronic weight management in pediatric patients ages 6 years and older with obesity due to: • POMC, PCSK1, or LEPR deficiency with variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) [see Clinical Studies (14.1)]. • BBS [see Clinical Studies (14.2)]. |

14 CLINICAL STUDIES

The safety and efficacy of IMCIVREE for chronic weight management in patients with obesity due to POMC, PCSK1, and LEPR deficiency were assessed in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period. Study 1 (NCT02836192) enrolled patients ages 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT03297660) enrolled patients ages 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency. In both studies, the local genetic testing results were centrally confirmed using Sanger sequencing. The studies enrolled patients with homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS for

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| 213783, 06/16/2022 | Setmelanotide (2) | Endocrinology | PCSK1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to:  
  - Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) [see Dosage and Administration (2.1)]  
  - Bardet-Biedl syndrome (BBS) [see Dosage and Administration (2.2)]. Limitations of Use:  
    - IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:  
      - Obesity due to suspected POMC, PCSK1, or LEPR deficiency with variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) [see Clinical Studies (14)]. (…)

| 213783, 06/16/2022 | Setmelanotide (3) | Endocrinology | POMC | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations | IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to:  
  - Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) [see Dosage and Administration (2.1)]  
  - Bardet-Biedl syndrome (BBS) [see Dosage and Administration (2.2)]. Limitations of Use:  
    - IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:  
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### Effect of IMCIVREE on Body Weight

In Study 1, 80% of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint, achieving a ≥10% weight loss after 1 year of treatment with IMCIVREE. In Study 2, 46% of patients with obesity due to LEPR deficiency achieved a ≥10% weight loss after 1 year of treatment with IMCIVREE (Table 2). (See Tables 2.3, and 4).
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<td>205123, 11/09/2017</td>
<td>Simeprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C [cytosine] to T [thymine] substitution) is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor. Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with OLYSIO-containing regimens. (See Table 12 and 13) 14 CLINICAL STUDIES 14.2 OLYSIO in Combination with Sofosbuvir Adult Subjects with HCV Genotype 1 Infection (…) These 59 subjects had a median age of 57 years (range 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, and 24% Black or African American; 46% had a BMI greater than or equal to 30 kg/m2; the median baseline HCV RNA level was 6.75 log10 IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0-F1, F2 and F3, respectively, and 29% had METAVIR fibrosis score F4 (cirrhosis); 75% had HCV genotype 1a of which 41% carried (…) These 59 subjects had a median age of 57 years (range 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, and 24% Black or African American; 46% had a BMI greater than or equal to 30 kg/m2; the median baseline HCV RNA level was 6.75 log10 IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0-F1, F2 and F3, respectively, and 29% had METAVIR fibrosis score F4 (cirrhosis); 75% had HCV genotype 1a of which 41% carried</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling
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### Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection

Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]), and subjects with IL28B CC and non-CC genotypes (43/46 [94%] and 107/112 [96%], respectively).

### 14.3 OLYSIO in Combination with Peg-IFN-alfa and RBV

Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection

(…) In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the OLYSIO and placebo treatment groups. The 785 enrolled subjects had a median age of 47 years (range: 18 to 73 years); 56% were male; 91% were White; 7% Black or African American; 1% Asian; and 17% Hispanic. 23% had a body mass index (BMI) greater than or equal to 30 kg/m²; 78% had baseline HCV RNA levels greater than 800000 IU/mL; 74% had METAVIR fibrosis score F3; 10% had METAVIR fibrosis score F4 (cirrhosis). 48% had HCV genotype 1a; 51% HCV genotype 1b; 29% had IL28B CC genotype; 56% IL28B CT genotype; and 15% IL28B TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a; in QUEST 2, 69% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b.

Table 20 shows the response rates in treatment-naïve adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR12 rates were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. (See Table 17) (…) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]), and subjects with IL28B CC and non-CC genotypes (43/46 [94%] and 107/112 [96%], respectively).

### 14.4 OLYSIO in Combination with Peg-IFN-alfa and RBV

Adult Subjects with HCV Genotype 1 Infection

(…) These 304 subjects had a median age of 45 years (range: 18 to 68 years; with 2% above 65 years); 49% were male; all were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater than or equal to 30 kg/m²; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 82% had METAVIR fibrosis score F0, F1 or F2, 12% METAVIR fibrosis score F3, and 6% METAVIR fibrosis score F4 (cirrhosis). 1% had HCV genotype 1a, and 95% HCV genotype 1b; less than 1% of the overall population had Q80K polymorphism at baseline; 95% had IL28B CC genotype; 20% IL28B CT genotype; and 1% IL28B TT genotype. Demographics and baseline characteristics were balanced across the OLYSIO 150 mg and placebo treatment groups.

### 14.5 OLYSIO in Combination with Peg-IFN-alfa and RBV

Adult Subjects with HCV Genotype 1 Infection who Failed Prior Peg-IFN-alfa and RBV Therapy

(…) Demographics and baseline characteristics were balanced between the OLYSIO and placebo treatment groups. The 393 subjects enrolled in the PROMISE trial had a median age of 52 years (range: 18 to 71 years; with 3% above 65 years); 66% were male; 94% were White, 3% Black or African American, 2% Asian, and 1% Hispanic. 26% had a BMI greater than or equal to 30 kg/m²; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 69% had METAVIR fibrosis score F0, F1 or F2, 15% METAVIR fibrosis score F3, and 15% METAVIR fibrosis score F4 (cirrhosis). 42% had HCV genotype 1a, and 58% HCV genotype 1b; 24% had IL28B CC genotype; 64% IL28B CT genotype; and 12% IL28B TT genotype; 13% of the overall population and 31% of the subjects with genotypes 1a and 1b had the NS3 Q80K polymorphism at baseline. The prior IFN-based HCV therapy was Peg-IFN-alfa-2a/RBV (65%) or Peg-IFN-alfa-2b/RBV (27%).

### 14.6 OLYSIO in Combination with Peg-IFN-alfa and RBV

SVR12 rates were higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype/subtype, baseline HCV RNA load (less than or equal to 800000 IU/mL), prior HCV therapy, METAVIR fibrosis score, and IL28B genotype. Table 20 shows the SVR rates by METAVIR fibrosis score. (…) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]), and subjects with IL28B CC and non-CC genotypes (43/46 [94%] and 107/112 [96%], respectively).

### 14.7 OLYSIO in Combination with Peg-IFN-alfa and RBV

SVR12 rates were higher in the OLYSIO-treated subjects compared to subjects receiving placebo in combination with Peg-IFN-alfa and RBV, regardless of HCV geno/subtype, METAVIR fibrosis score, and IL28B genotype. (See Table 21) (…) The 106 enrolled subjects in the C212 trial had a median age of 48 years (range: 27 to 67 years; with 2% above 65 years); 85% were male; 82% were White, 14% Black or African American, 1% Asian, and 6% Hispanic; 12% had a BMI greater than or equal to 30 kg/m²; 88% had baseline HCV RNA levels greater than 800000 IU/mL; 68% had METAVIR fibrosis score F0, F1 or F2, 15% METAVIR fibrosis score F3, and 10% METAVIR fibrosis score F4; 82% had HCV genotype 1a, and 17% HCV genotype 1b; 28% of the overall population and 34% of the subjects with genotype 1a had Q80K polymorphism at baseline; 27% had IL28B CC genotype, 16% IL28B CT genotype, and 17% IL28B TT genotype. 100% of (n=63) were HCV treatment-naïve subjects, 14% (n=15) prior relapsers, 9% (n=10) prior partial responders, and 26% (n=28) prior null responders. (…) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]), and subjects with IL28B CC and non-CC genotypes (43/46 [94%] and 107/112 [96%], respectively).

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<td>209884, 06/21/2022</td>
<td>Siponimod</td>
<td>Neurology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Contraindications, Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>(…) The 107 enrolled subjects in the RESTORE trial with HCV genotype 4 had a median age of 49 years (range: 27 to 69 years; with 5% above 65 years); 79% were male; 72% were White, 28% Black or African American, and 7% Hispanic; 14% had a BMI greater than or equal to 30 kg/m²; 60% had baseline HCV RNA levels greater than 800,000 IU/mL; 57% had METAVIR fibrosis score F0, F1 or F2, 14% METAVIR fibrosis score F3, and 26% METAVIR fibrosis score F4; 42% had HCV genotype 4a, and 24% had HCV genotype 4d; 8% had IL28B CC genotype, 58% IL28B CT genotype, and 35% IL28B TT genotype. (…)</td>
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<tr>
<td>203922, 10/19/2017</td>
<td>Sodium Nitrite (1)</td>
<td>Toxicology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. After stopping MAYZENT treatment, residual lowering effects on peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose. [see Warnings and Precautions (5.1)].</td>
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</table>
| 203922, 10/19/2017                     | Sodium Nitrite (2) | Toxicology | Non-specific (Con genital Methemoglobinemia) | Boxed Warning, Warnings and Precautions | **BOXED WARNING**
**WARNING: LIFE THREATENING HYPOTENSION AND METHEMOGLOBIN FORMATION**
Sodium nitrite can cause serious adverse reactions and death in humans, even at doses less than twice the recommended therapeutic dose. Sodium nitrite causes hypotension and methemoglobin formation, which diminishes oxygen carrying capacity. Hypotension and methemoglobin formation can occur concurrently or separately. Because of these risks, sodium nitrite should be used to treat acute life-threatening cyanide poisoning and be used with caution in patients where diagnosis of cyanide poisoning is uncertain. Patients should be closely monitored to ensure adequate perfusion and oxygenation during treatment with sodium nitrite. Alternative therapeutic approaches should be considered in patients known to have diminished oxygen or cardiovascular reserve (e.g., smoking, smoking victims, pre-existing anemia, cardiac or respiratory compromise), and those at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency, e.g., congenital methemoglobin reductase deficiency) as they are at greater risk for potentially life-threatening adverse events related to the use of sodium nitrite. [see Warnings and Precautions (5.1 and 5.2)]. |

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<tr>
<td>07/29/2022</td>
<td>60023/0000/ANDA/0001</td>
<td>Sodium Oxybate</td>
<td>Neurology</td>
<td>ALDH5A1</td>
<td>Indications and Usage, Dosage Administration, Adverse Reactions, Clinical Pharmacology</td>
<td>4 CONTRAINDICATIONS: Xyrem is contraindicated for use in: • combination with sedative hypnotics [see Warnings and Precautions (5.1)]; • combination with alcohol [see Warnings and Precautions (5.1)]; • patients with succinic semialdehyde dehydrogenase deficiency [see Clinical Pharmacology (12.3)].</td>
</tr>
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</table>
| 02/11/2021 | 021196, 09/25/2020    | Sodium Phenylbutyrate       | Metabolism         | ASS1, CPS1, OTC (Urea Cycle Disorders) | Indications and Usage, Dosage Administration, Adverse Reactions, Clinical Pharmacology | 5.2 Methemoglobinemia: Supportive care alone may be sufficient treatment without administration of antidotes for many cases of cyanide intoxication, particularly in conscious patients without signs of severe toxicity. Monitor patients closely to ensure adequate perfusion and oxygenation during treatment with sodium nitrite. Monitor methemoglobin levels and administer oxygen during treatment with sodium nitrite whenever possible. When sodium nitrite is administered to humans a wide range of methemoglobin concentrations occur. (…)

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In patients with urea cycle disorders, BUPHENYL decreased elevated plasma ammonia glutamine levels. It increases waste nitrogen excretion in the form of phenylacetylglutamine.

Hepatic insufficiency:

In patients who did not have urea cycle disorders but had impaired hepatic function, the metabolism and excretion of sodium phenylbutyrate were not affected. However, this information was obtained from unvalidated, uncontrolled case studies.

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<td>0528/2021, 214665</td>
<td>Sotorasib</td>
<td>Oncology</td>
<td>KRAS</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>LUMAKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test [see Dosage and Administration (2.1)], who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).</td>
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<tr>
<td>060076</td>
<td>Streptomycin</td>
<td>Infectious Diseases</td>
<td>MT-RNR1</td>
<td>Warnings</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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</table>
| 019998, 10/02/2016 | Succimer | Hematology | G6PD | Clinical Pharmacology | CLINICAL PHARMACOLOGY: (...) In addition to the controlled studies, approximately 250 patients with lead poisoning have been treated with succimer either orally or parenterally in open U.S. and foreign studies with similar results reported. Succimer has been used for the treatment of lead poisoning in one patient with sickle cell anemia and in five patients with glucose-6-phosphatase deficiency without adverse reactions. (…)

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| 008453, 11/01/2022                     | Succinylcholine | Anesthesiology | CACNA1S, RYR1 (Genetic Susceptibility to Malignant Hyperthermia) | Boxed Warning, Contraindications, Warnings, Precautions, Adverse Reactions | **Reduced Plasma Cholinesterase Activity**  
Succinylcholine should be used carefully in patients with reduced plasma cholinesterase (pseudochoolinesterase) activity. The likelihood of prolonged neuromuscular block following administration of succinylcholine must be considered in such patients (see DOSAGE AND ADMINISTRATION).  
Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for atypical plasma cholinesterase gene), pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. (…)  
(…) Patients homozygous for atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine. In these patients, a 5- to 10-mg test dose of succinylcholine may be administered to evaluate sensitivity to succinylcholine, or neuromuscular blockade may be produced by the cautious administration of a 1-mg/ml solution of succinylcholine by slow IV infusion. Apnea or prolonged muscle paralysis should be treated with controlled respiration. |

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| Sulfadiazine | Infectious Diseases | G6PD | Warnings | WARNINGS
The use of SILVADENE Cream 1% (sulfa-diazine) in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur. |
| Sulfamethoxazole and Trimethoprim (1) | Infectious Diseases | G6PD | Precautions | PRECAUTIONS
Hemolysis in glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see Clinical Pharmacology and Dosage and Administration). |
| Sulfamethoxazole and Trimethoprim (2) | Infectious Diseases | Nonspecific (NAT) | Precautions | PRECAUTIONS
Electrolyte Abnormalities
During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides. |
| Sulfasalazine (1) | Gastroenterology | G6PD | Precautions | PRECAUTIONS
General
AZULFIDINE EN-tabs Tablets should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anaemia. This reaction is frequently dose-related. If toxic or hypersensitivity reactions occur, AZULFIDINE EN-tabs should be discontinued immediately. |
| Sulfasalazine (2) | Gastroenterology | Nonspecific (NAT) | Clinical Pharmacology | CLINICAL PHARMACOLOGY
Pharmacokinetics
Metabolism: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a nonacetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible. Special Populations
Acetylator Status: The metabolism of SP to AcSP is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life of SP (14.8 hours vs 10.4 hours) and an accumulation of higher plasma levels of SP than fast acetylators. The clinical implication of this is unclear; however, in a small pharmacokinetic trial where acetylator status was determined, subjects who were slow acetylators of SP showed a higher incidence of adverse events. |

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007073, 03/04/2014

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</table>
| 017381, 08/01/2016 | Sulfadiazine | Infectious Diseases | G6PD | Warnings | WARNINGS
The use of SILVADENE Cream 1% (sulfa-diazine) in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur. |
| 017377, 04/30/2021 | Sulfamethoxazole and Trimethoprim (1) | Infectious Diseases | G6PD | Precautions | PRECAUTIONS
Hemolysis in glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see Clinical Pharmacology and Dosage and Administration). |
| 017377, 04/30/2021 | Sulfamethoxazole and Trimethoprim (2) | Infectious Diseases | Nonspecific (NAT) | Precautions | PRECAUTIONS
Electrolyte Abnormalities
During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides. |
| 007073, 03/04/2014 | Sulfasalazine (1) | Gastroenterology | G6PD | Precautions | PRECAUTIONS
General
AZULFIDINE EN-tabs Tablets should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anaemia. This reaction is frequently dose-related. If toxic or hypersensitivity reactions occur, AZULFIDINE EN-tabs should be discontinued immediately. |
| 007073, 03/04/2014 | Sulfasalazine (2) | Gastroenterology | Nonspecific (NAT) | Clinical Pharmacology | CLINICAL PHARMACOLOGY
Pharmacokinetics
Metabolism: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a nonacetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible. Special Populations
Acetylator Status: The metabolism of SP to AcSP is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life of SP (14.8 hours vs 10.4 hours) and an accumulation of higher plasma levels of SP than fast acetylators. The clinical implication of this is unclear; however, in a small pharmacokinetic trial where acetylator status was determined, subjects who were slow acetylators of SP showed a higher incidence of adverse events. |

020992, 11/30/2020

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<th>Labeling Text‡</th>
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</table>
| 020992, 11/30/2020 | Synthetic Conjugated Estrogens, A (1) | Gynecology | PROC | Contraindications | 4 CONTRAINDICATIONS
CENESTIN is contraindicated in women with any of the following conditions:
• Undiagnosed abnormal genital bleeding [see Warnings and Precautions (5.2)].
• Breast cancer or a history of breast cancer [see Warnings and Precautions (5.2)].
• Estrogen-dependent neoplasia [see Warnings and Precautions (5.2)].
• Active DVT, PE, or a history of these conditions [see Warnings and Precautions (5.1)].
• Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions [see Warnings and Precautions (5.1)].
• Known anaphylactic reaction or angioedema or hypersensitivity to CENESTIN.
• Hepatic impairment or disease.
• Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders. |
| 020992, 11/30/2020 | Synthetic Conjugated Estrogens, A (2) | Gynecology | PROS1 | Contraindications | 4 CONTRAINDICATIONS
CENESTIN is contraindicated in women with any of the following conditions:
• Undiagnosed abnormal genital bleeding [see Warnings and Precautions (5.2)].
• Breast cancer or a history of breast cancer [see Warnings and Precautions (5.2)].
• Estrogen-dependent neoplasia [see Warnings and Precautions (5.2)].
• Active DVT, PE, or a history of these conditions [see Warnings and Precautions (5.2)].
• Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions [see Warnings and Precautions (5.1)].
• Known anaphylactic reaction or angioedema or hypersensitivity to CENESTIN.
• Hepatic impairment or disease.
• Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders. |
| 020992, 11/30/2020 | Synthetic Conjugated Estrogens, A (3) | Gynecology | SERPIN1 (Antithrombin III) | Contraindications | 4 CONTRAINDICATIONS
CENESTIN is contraindicated in women with any of the following conditions:
• Undiagnosed abnormal genital bleeding [see Warnings and Precautions (5.2)].
• Breast cancer or a history of breast cancer [see Warnings and Precautions (5.2)].
• Estrogen-dependent neoplasia [see Warnings and Precautions (5.2)].
• Active DVT, PE, or a history of these conditions [see Warnings and Precautions (5.1)].
• Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions [see Warnings and Precautions (5.1)].
• Known anaphylactic reaction or angioedema or hypersensitivity to CENESTIN.
• Hepatic impairment or disease.
• Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders. |

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<td>211996, 05/03/2019</td>
<td>Tafamidis</td>
<td>Cardiology</td>
<td>TTR</td>
<td>Clinical Pharmacology, Clinical Studies</td>
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<td>12. CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics</td>
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|                                        |               |                   |            | A proprietary TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer ex vivo. The TTR stabilization assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre- and post-treatment with 2-day in vitro denaturation with urea. Using this proprietary assay, a dose-dependent trend for greater TTR tetramer stabilization is observed for VYNDAQEL 80-mg compared to VYNDAQEL 20-mg. However, the clinical relevance of a higher TTR tetramer stabilization towards cardiovascular outcomes is not known. VYNDAQEL stabilized both the wild type TTR tetramer and the tetrarsers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilized the TTR tetramer for 25 variants tested ex vivo. (…)
|                                        |               |                   |            | 14 CLINICAL STUDIES |
|                                        |               |                   |            | Efficacy was demonstrated in a multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (NCT01994889). Patients were randomized in a 1:2:2 ratio to receive VYNDAQEL 20 mg (n=88), VYNDAQEL 80 mg (administered as four 20-mg VYNDAQEL capsules) (n=176), or matching placebo (n=177) once daily for 30 months, in addition to standard of care (e.g., diuretics). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as baseline disease severity (NYHA Class). Transplant patients were excluded from this study. Table 1 describes the patient demographics and baseline characteristics. (See Tables 1 and 3, Figures 1 and 4)
|                                        |               |                   |            | |
| 210607, 08/08/2018                     | Tafenoquine   | Infectious Diseases | G6PD       | 2 DOSAGE AND ADMINISTRATION |
|                                        |               |                   |            | 2.1 Tests to be Performed Prior to ARAKODA Dose Initiation |
|                                        |               |                   |            | All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA [see Contraindications (4), Warnings and Precautions (5.1)]. |
|                                        |               |                   |            | 4 CONTRAINDICATIONS |
|                                        |               |                   |            | ARAKODA is contraindicated in: |
|                                        |               |                   |            | • patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia [see Warnings and Precautions (5.2)]. |
|                                        |               |                   |            | • breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown [see Warnings and Precautions (5.3), Use in Specific Populations (8.2)]. |
|                                        |               |                   |            | 5 WARNINGS AND PRECAUTIONS |
|                                        |               |                   |            | 5.1. Hemolytic Anemia |
|                                        |               |                   |            | Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA [see Contraindications (4)]. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status [see Contraindications (4)]. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients [see Adverse Reactions (6.1)]. Monitor patients for clinical signs or symptoms of hemolysis [see Warnings and Precautions (5.6)]. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur. |
|                                        |               |                   |            | 5.2 G6PD Deficiency in Pregnancy and Lactation |
|                                        |               |                   |            | Potential Harm to the Fetus |
|                                        |               |                   |            | The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus may be G6PD-deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Use in Specific Populations (8.1 and 8.3)]. |
|                                        |               |                   |            | Potential Harm to the Breastfeeding Infant |
|                                        |               |                   |            | A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown [see Contraindications (4)]. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose [see Use in Specific Populations (8.2)]. |
|                                        |               |                   |            | 8 USE IN SPECIFIC POPULATIONS |
|                                        |               |                   |            | 8.1 Pregnancy Risk Summary |
|                                        |               |                   |            | The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Warnings and Precautions (5.2)]. (…)
|                                        |               |                   |            | 8.2 Lactation Risk Summary |

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A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown (see Contraindications (4) and Clinical Considerations). There is no information regarding the presence of ARAKODA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition.

Clinical Considerations
Check the infant’s G6PD status before maternal breastfeeding commences. If an infant is G6PD deficient, exposure to ARAKODA during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency or whose G6PD status is unknown, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose of ARAKODA.

8.3 Females and Males of Reproductive Potential
Contraception
ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus (see Warnings and Precautions (5.2), Use in Specific Populations (8.1)). Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA.

17 PATIENT COUNSELING INFORMATION
G6PD Testing and Hemolytic Anemia
Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia (see Warnings and Precautions (5.1)).

Lactation
Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose (see Contraindication (4), Warnings and Precautions (5.2), Use in Specific Populations (8.2)).

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<tr>
<td>211651, 06/20/2023</td>
<td>Talazoparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA (see Dosage and Administration (1.1)).</td>
</tr>
</tbody>
</table>

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Information on the FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics. gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer

2.2 Recommended Dosage for gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer
The recommended dosage of TALZENNA is 1 mg taken orally once daily, until disease progression or unacceptable toxicity.

2.5 Dosage Modifications for Adverse Reactions

gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer
See Tables 1 and 3

2.6 Recommended Dosage in Patients with Renal Impairment
gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer
The recommended dosage of TALZENNA is 1 mg taken orally once daily [see Use in Specific Populations (8.7)].

2.7 Dosage Modifications for P-glycoprotein Inhibitors
gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer
Avoid coadministration of TALZENNA with the following P-glycoprotein (P-gp) inhibitors: irinotecan, amiodarone, cerdulatin, clarithromycin, irinotecan, and verapamil. If coadministration of TALZENNA with these P-gp inhibitors cannot be avoided, reduce the dose of TALZENNA to 0.75 mg taken orally once daily. When the P-gp inhibitor is discontinued, increase the dose of TALZENNA (after 3 – 5 half-lives of the P-gp inhibitor) to the dose of TALZENNA that was used before starting the P-gp inhibitor [see Drug Interactions (7.1)].

2.9 Clinical Trials Experience
Treatment of gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer

EMBRACA

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| 211651, 06/20/2023 | Talazoparib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (n=286) or a chemotherapy agent (capecitabine, erublin, gemcitabine, or vinorelbine) of the healthcare provider’s choice (n=126) until disease progression or unacceptable toxicity. (…) |

### 14 CLINICAL STUDIES

#### 14.1 Deleterious or Suspected Deleterious Germline BRCA-mutated HER2-negative Locally Advanced or Metastatic Breast Cancer

EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive TALZENNA 1 mg or healthcare provider’s choice of chemotherapy (capecitabine, erublin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer (TNBC) versus non-TNBC), and by central nervous system (CNS) metastasis (yes versus no). (…) No prior treatment with a PARP inhibitor was permitted. Of the 431 patients randomized in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious gBRCAm using a clinical trial assay; out of which 354 (82%) were confirmed using the BRACAnalysis CDx®. BRCA mutation status (breast cancer susceptibility gene 1 (BRCA1) positive or breast cancer susceptibility gene 2 (BRCA2) positive) was similar across both treatment arms. (…) |

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<td>211651, 06/20/2023</td>
<td>Talazoparib (3)</td>
<td>Oncology</td>
<td>Homologous Recombination Repair</td>
<td>Indications and Usage</td>
<td>TAZLENNA is indicated in combination with enzalutamide for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) [see Dosage and Administration (2.3)].</td>
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1 INDICATIONS AND USAGE
1.3 HRR Gene-mutated mCRPC

TAZLENNA is indicated in combination with enzalutamide for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) [see Dosage and Administration (2.3)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on the FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics. HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Select patients for the treatment of HRR gene-mutated mCRPC with TALZENNA based on the presence of HRR gene mutations (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C) [see Indications and Usage (1.2), Clinical Studies (14.2)].

An FDA-approved test for the detection of HRR gene mutations for use with TALZENNA is not currently available.

2.3 Recommended Dosage for HRR Gene-mutated mCRPC

The recommended dosage of TALZENNA is 0.5 mg taken orally once daily in combination with enzalutamide until disease progression or unacceptable toxicity. Refer to the enzalutamide prescribing information for recommended enzalutamide dosing information. Patients receiving TALZENNA and enzalutamide should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchectomy.

2.5 Dosage Modifications for Adverse Reactions

HRR Gene-mutated mCRPC

See Tables 2 and 3

2.6 Recommended Dosage in Patients with Renal Impairment

HRR Gene-mutated mCRPC

The recommended dosage of TALZENNA for patients with severe renal impairment (Ccr 15 - 29 mL/min) is 0.25 mg taken orally once daily in combination with enzalutamide [see Use in Specific Populations (8.7)].

The recommended dosage of TALZENNA for patients with severe renal impairment (Ccr 15 - 29 mL/min) is 0.25 mg taken orally once daily in combination with enzalutamide [see Use in Specific Populations (8.7)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

HRR Gene-mutated mCRPC

The safety of TALZENNA in combination with enzalutamide was evaluated in patients with HRR gene-mutated mCRPC enrolled in TALAPRO-2 [see Clinical Studies (14.2)]. Patients were randomized to receive either TALZENNA 0.5 mg in combination with enzalutamide 160 mg once daily (n=197), or placebo in enzalutamide 160 mg once daily (n=199) until disease progression or unacceptable toxicity. Among patients receiving TALZENNA, 86% were exposed for 6 months or longer, 60% were exposed for greater than one year, and 18% were exposed for greater than two years. (…)

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TALZENNA

Effect of P-gp Inhibitors

HRR Gene-mutated mCRPC

The effect of coadministration of P-gp inhibitors on talazoparib exposure when TALZENNA is taken in combination with enzalutamide has not been studied.

Monitor patients for increased adverse reactions and modify the dosage as recommended for adverse reactions when TALZENNA is coadministered with a P-gp inhibitor [see Dosage and Administration (2.5)].

14 CLINICAL STUDIES

14.2 HRR Gene-mutated mCRPC

The efficacy of TALZENNA in combination with enzalutamide was evaluated in TALAPRO-2 (NCT03395197), a randomized, double-blind, placebo-controlled, multi-cohort trial in which 399 patients with HRR gene-mutated (mCRPC) enrolled in TALAPRO-2 [see Clinical Studies (14.2)]. Patients were randomized to receive either TALZENNA 0.5 mg in combination with enzalutamide 160 mg once daily (n=197), or placebo in enzalutamide 160 mg once daily (n=199) until disease progression or unacceptable toxicity. Among patients receiving TALZENNA, 86% were exposed for 6 months or longer, 60% were exposed for greater than one year, and 18% were exposed for greater than two years. (…)

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| 021807, 04/08/2019        | Tamoxifen (1) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer
SOLTAMOX is indicated for the treatment of adult patients with estrogen receptor-positive metastatic breast cancer.

1.2 Adjuvant Treatment of Breast Cancer
SOLTAMOX is indicated:
• for the adjuvant treatment of adult patients with early stage estrogen receptor-positive breast cancer
• to reduce the occurrence of contralateral breast cancer in adult patients when used as adjuvant therapy for the treatment of breast cancer.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Astranorlizone Adjuvant Trial (ATAC, Anitrexol, Tamoxifen, Alone or in Combination) – Study of Astranorlizone Compared to Tamoxifen for Adjuvant Treatment of Early Breast Cancer
At a median follow-up of 33 months, the combination of anastranolizone and tamoxifen did not demonstrate an efficacy benefit when compared to tamoxifen monotherapy in all patients as well as in the hormone receptor-positive subpopulation. The combination treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving anastranolizone 1 mg and tamoxifen 20 mg monotherapy, respectively. (…)

12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
The impact of CYP2D polymorphisms on the efficacy of tamoxifen is well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women’s Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p<0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.

14 CLINICAL STUDIES
14.2 Adjuvant Treatment of Breast Cancer
The Early Breast Cancer Trials’ Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, 1995, 1998 and 2011. The 10-year outcome data were reported in 1998 for 36,689 women in 55 randomized trials of another formulation of adjuvant tamoxifen using doses of 20 to 40 mg per day for 1 to 5+ years. Twenty-five percent of patients received 1 year or less of trial treatment, 52% received 2 years, and 23% received 5 years of trial treatment. Forty-eight percent of tumors were estrogen receptor (ER) positive (>10 fmol/mg), 21% were ER-poor (<10 fmol/mg), and 31% were ER-unknown. Among 29,441 patients with ER-positive or ER-unknown breast cancer, 58% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node-positive disease and 46% had node-negative disease.

In women with ER-positive or ER-unknown breast cancer:
• With positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for tamoxifen vs. 50.5% for control (log-rank 2p <0.00001). The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (log-rank 2p <0.00001).
• With negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (log-rank 2p <0.00001). The recurrence-free rate at 10 years was 79.2% for tamoxifen vs. 64.3% for control (log-rank 2p <0.00001).
• Who received 1 year or less, 2 years, or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17%, and 26%, respectively (2p <0.003). The corresponding reductions in breast cancer recurrence were 21%, 29%, and 47% (2p <0.00001).

Results in patients with ER-poor breast cancer:
• Benefit is less clear for women with ER-poor breast cancer in whom the proportional reduction in recurrence was 10% (2p = 0.007) for all durations taken together, or 9% (2p = 0.02) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (not significant).

Node-positive: Individual Studies
(… ) In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50 to 59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while survival results were poorer in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60 to 70 years, there was an improvement in disease-free survival with tamoxifen without any clear relationship to estrogen or progesterone receptor status. (…)

Node-negative: Individual Studies
NSABP B-14, a prospective, double-blind, randomized study, compared another formulation of tamoxifen to placebo as adjuvant therapy in women with axillary node-negative, estrogen-receptor-positive (≥10 fmol/mg cytosol protein) breast cancer (following total mastectomy and axillary dissection, or segmental mastectomy and axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50.

One additional randomized study (NATO) demonstrated improved disease-free survival for another formulation of tamoxifen compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of tamoxifen appeared to be independent of estrogen receptor status.

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<td>Oncology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Thromboembolic Events (…) In a small substudy (N = 81) of the NSABP-1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations G20210A as a means to identify those who may not be appropriate candidates for tamoxifen therapy. (…)</td>
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<td>021807, 04/08/2019</td>
<td>Tamsulosin (4)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetic Metabolism Tamsulosin is extensively metabolized by CYP450 enzymes, including CYP3A, CYP2D6, CYP2C9, CYP2C19, and CYP2B6. N-desmethyltamsulosin, formed predominantly by CYP3A, is the major metabolite found in plasma. The pharmacological activity of N-desmethyltamsulosin is similar to that of tamsulosin. Endoxifen and 4-hydroxytamsulosin, identified as minor metabolites, have 100-fold greater affinity for the estrogen receptor and 30- to 100-fold greater potency in suppressing estrogen-dependent cell proliferation than tamsulosin. The polymorphic enzyme CYP2D6 is involved in the formation of endoxifen and 4-hydroxytamsulosin, and it is the key enzyme that catalyzes the formation of endoxifen from N-desmethyltamsulosin. Endoxifen concentrations may differ among patients because of various CYP2D6 genotypes (see Clinical Pharmacology [12.5]). Phase 2 enzymes, such as SULT1A1, UGT2B7, and UGT1A4, are associated with tamsulosin clearance from plasma.</td>
</tr>
<tr>
<td>020579, 01/23/2019</td>
<td>Tamsulosin</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Adverse Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Drug Interactions Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6. FLOMAX capsules 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. FLOMAX capsules should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terofarline) inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers particularly at a dose higher than 0.4 mg (e.g., 0.8 mg) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. (…)</td>
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<td></td>
<td>1 INDICATIONS AND USAGE</td>
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<td>KIMMTRAK is indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>Select patients for treatment of unresectable or metastatic uveal melanoma with KIMMTRAK based on a positive HLA-A<em>02:01 genotyping test [see Clinical Studies (14)]. An FDA-approved test for the detection of HLA-A</em>02:01 genotyping is not currently available.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>KIMMTRAK was evaluated in IMCgp100-202, a randomized, open-label, multicenter trial (NCT03070392) that enrolled patients with metastatic uveal melanoma [N=376]. Patients were required to be HLA-A*02:01 genotype positive identified by a central assay.</td>
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<td>14.2 Treatment-Naïve Adults</td>
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<td>12.5 Pharmacogenomics</td>
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<td>A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR). rs12979860 was genotyped in 454 of 1088 subjects in Trial 108 (treatment-naïve) and 527 of 662 subjects in Trial C216 (previously treated) [see Clinical Studies (14.2 and 14.3) for trial descriptions]. SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naïve subjects receiving PR48 [Table 9]. Among both treatment-naïve and previous treatment failures, subjects of all IL28B genotypes appeared to have higher SVR rates with regimens containing INCIVEK. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the subtrial population relative to the overall trial population. In Trial C211, all subjects were prospectively tested for IL28B variants; there were no clinically relevant differences in SVR12 responses between qd and twice-daily dosing within the genetic subgroups (see Table 9)</td>
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<td>Trial C211 (OPTIMIZE)</td>
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<td>(…) SVR rates were similar for the T12 (twice daily)/PR and T12 (qd)/PR groups across subgroups determined by sex, age, race, ethnicity, body mass index, HCV genotype subtype, IL28B genotype, baseline HCV RNA (less than 800,000, greater than or equal to 800,000 IU per mL), and extent of liver fibrosis. However, there were small numbers of subjects enrolled in some key subgroups.</td>
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<td>ALK</td>
<td>Clinical Studies</td>
<td>The efficacy of TEPMETKO was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring METex14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. (...).</td>
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| 02/03/2021, 214096 | Tepotinib (3) | Oncology | MET | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
TEPMETKO is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. |

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to TEPMETKO in 448 patients with solid tumors enrolled in five open-label, single-arm studies receiving TEPMETKO as single agent at a dose of 450 mg once daily. This included 255 patients with NSCLC positive for METex14 skipping alterations, who received TEPMETKO in VISION. Among 448 patients who received TEPMETKO, 32% were exposed for 6 months or longer, and 12% were exposed for greater than one year. The data described below reflect exposure to TEPMETKO 450 mg once daily in 255 patients with metastatic non-small cell lung cancer (NSCLC) with METex14 skipping alterations in VISION [see Clinical Studies (14)]. (See Table 2) (...). |

6.5 Geriatric Use

Of 255 patients with METex14 skipping alterations in VISION who received 450 mg TEMETKO once daily, 79% were 65 years or older, and 43% were 75 years or older. No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients. |

14 CLINICAL STUDIES

The efficacy of TEPMETKO was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring METex14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. The identification of METex14 skipping alterations was prospectively determined using central laboratories employing either a PCR-based or next-generation sequencing-based clinical trial assay using tissue (58%) and/or plasma (65%) samples. (...). |

### Toxicities

Based on findings from a Phase 1/2 study in patients with advanced solid tumors and on responses from single-arm studies, the most common AEs (≥25% of patients) were neutropenia (69%), fatigue (57%), anemia (55%), and diarrhea (39%). Other toxicities included thrombocytopenia, neutrophil count decreased, elevated alanine aminotransferase, and AST. Adverse events were usually managed with dose modifications, interruptions, and dose reductions. The most common drug-related AEs (≥4% of patients) were neutropenia (57%), fatigue (39%), neutropenia (37%), and diarrhea (37%).

### Pharmacokinetics

TEPMETKO has a terminal half-life of approximately 36 hours, with a volume of distribution of approximately 20 liters. The pharmacokinetics of TEPMETKO are linear and dose-proportional over the range of 400 mg to 800 mg once daily.

### Nonclinical Pharmacology

TEPMETKO has been shown to reduce the expression of MET protein and MET messenger RNA in vitro and in vivo.

### Clinical Pharmacology

TEPMETKO is a small molecule inhibitor of MET, a receptor tyrosine kinase that is involved in the growth and proliferation of cancer cells. MET is overexpressed in a variety of cancer types, including NSCLC.

### Dosage and Administration

2.1 Administration

TEPMETKO is administered orally once daily with food. The usual dose is 450 mg once daily, administered as a single 450 mg tablet or multiple 45 mg tablets (1.5 x 30 mg tablets). The dose may be reduced to 300 mg once daily for patients with severe renal impairment (creatinine clearance <30 mL/min).

2.2 Individualized Dosing

Dosing recommendations are based on individual patient characteristics, including renal function, hepatic function, and genetic factors.

### Precautions

2.3 Precautions

TEPMETKO is associated with increased risk of myelosuppression, particularly neutropenia. Patients should be monitored for hematologic toxicity, and dose adjustments may be necessary.

### Warnings and Precautions

2.4 Warnings and Precautions

TEPMETKO is contraindicated in patients with known hypersensitivity to any component of the formulation. It is also contraindicated in patients with uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor.

### Indications and Usage

TEPMETKO is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

### Notes

- Poor CYP2D6 Metabolizers
- Extensive and Intermediate CYP2D6 Metabolizers
- Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, XENAZINE should then be individualized accordingly to their status as PMs or EMs [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
- Dosing Recommendations Above 50 mg per day Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
- Extensive and Intermediate CYP2D6 Metabolizers
- Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse reactions such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants) [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)] Poor CYP2D6 Metabolizers

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| 012429, 05/23/2018 | Thioguanine (1) | Oncology | TPMT | Dosage and Administration,Warnings,Precautions,Clinical Pharmacology | **5 WARNINGS AND PRECAUTIONS**

## 5.3 Laboratory Tests

Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are poor metabolizers (PMs), extensive (EMs) or intermediate metabolizers (IMs) of XENAZINE.

 Patients who are PMs of XENAZINE will have substantially higher levels of exposure to the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient’s CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.7 Poor or Extensive CYP2D6 Metabolizers

Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

**Poor Metabolizers**

Poor CYP2D6 metabolizers (PM) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) compared to EMs. The dosage should, therefore, be adjusted according to a patient’s CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

**Extensive / Intermediate Metabolizers**

In extensive (EMs) or intermediate metabolizers (IMs), the dosage of XENAZINE can be titrated to a maximum single dose of 37.5 mg and a recommended maximum daily dose of 100 mg [see Dosage and Administration (2.2), Drug Interactions (7.1), Clinical Pharmacology (12.3)].

### 12 CLINICAL PHARMACOLOGY

#### 12.3 Pharmacokinetics

**Specific Populations**

Poor CYP2D6 Metabolizers

Although the pharmacokinetics of XENAZINE and its metabolites in patients who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively) [see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.7)].

**Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].**

#### 8.7 Poor or Extensive CYP2D6 Metabolizers

Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

**Poor Metabolizers**

Poor CYP2D6 metabolizers (PM) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) compared to EMs. The dosage should, therefore, be adjusted according to a patient’s CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

**Extensive / Intermediate Metabolizers**

In extensive (EMs) or intermediate metabolizers (IMs), the dosage of XENAZINE can be titrated to a maximum single dose of 37.5 mg and a recommended maximum daily dose of 100 mg [see Dosage and Administration (2.2), Drug Interactions (7.1), Clinical Pharmacology (12.3)].

### 12 CLINICAL PHARMACOLOGY

#### 12.3 Pharmacokinetics

**Specific Populations**

Poor CYP2D6 Metabolizers

Although the pharmacokinetics of XENAZINE and its metabolites in patients who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively) [see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.7)].

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#### 8.7 Poor or Extensive CYP2D6 Metabolizers

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Blue text represents the most recent additions and/or changes since last posted version.
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<tbody>
<tr>
<td>012429, 05/23/2018</td>
<td>Thioguanine (2)</td>
<td>Oncology</td>
<td>NUDT15</td>
<td>Dosage and Administration</td>
<td>Patients with homozgyous deficiency of either TPMT or NUDT15 enzyme typically require 10% or less of the standard thioguanine dosage. Reduce initial dosage in patients who are known to have homozgyous TPMT or NUDT15 deficiency. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. Reduce the dosage based on tolerability.</td>
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<tr>
<td>011808</td>
<td>Thioridazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Contraindications, Warnings, Precautions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<td>022433, 04/03/2019</td>
<td>Ticagrelor</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenetics In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status.</td>
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<tr>
<td>207981, 08/02/2023</td>
<td>Tipiracil and Trifluridine (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.2 Metastatic Gastric Cancer LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.</td>
</tr>
</tbody>
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<td>207981, 02/02/2023</td>
<td>Tipiracil and Trifluridine (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td></td>
<td></td>
<td></td>
<td>1.1 Metastatic Colorectal Cancer</td>
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<td>LONSURF, as a single agent or in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.</td>
</tr>
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<td></td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Metastatic Colorectal Cancer</td>
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<td>Previously treated metastatic colorectal cancer (single agent LONSURF) RECOURSE The efficacy of LONSURF was evaluated in RECOURSE (NCT01605907), an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (mCRC). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG performance status (PS) 0-1, absence of brain metastases, and absence of ascites requiring drainage in the past four weeks. Patients were randomized 2:1 to receive LONSURF 35 mg/m2 or matching placebo orally twice daily after meals on Days 1-5 and 8-12 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (&lt;18 months vs. ≥18 months), and region (Japan vs. US, Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS). A total of 600 patients were randomly assigned to LONSURF (N=303) with best supportive care (BSC) or matching placebo (N=297) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian, respectively, and all patients had baseline ECOG PS 0-1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab.</td>
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<td>Efficacy results are summarized in Table 1 and Figure 3.</td>
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<td>Previously treated metastatic colorectal cancer (LONSURF in combination with bevacizumab) SCHENGY The efficacy of LONSURF in combination with bevacizumab was evaluated in SCHENGY (NCT04737187), an international, randomized (1:1), open-label study in patients with previously treated metastatic colorectal cancer. Patients were required to have received no more than 2 prior treatments for advanced disease, including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (optionally) and an anti-EGFR monoclonal antibody for patients with RAS wild-type. Other key eligibility criteria included ECOG performance status (PS) 0-1, absence of symptomatic brain metastases, absence of ascites requiring drainage in the past 4 weeks, absence of uncontrolled hypertension, absence of non-healing wound, and absence of deep venous thromboembolic event in the past 4 weeks. Patients were randomized to receive LONSURF 35 mg/m2 administered orally twice daily on Days 1 to 5 and 8 to 12 of each 28-day cycle with or without bevacizumab 5 mg/kg administered intravenously every 2 weeks (on Day 1 and Day 15) of each 4-week cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (North America, European Union, Rest of the World), time since diagnosis of metastatic disease (&lt;18 months vs. ≥18 months) and RAS status (wild-type, mutant). The major efficacy outcome measure was overall survival (OS), and an additional efficacy outcome measure was progression-free survival (PFS). A total of 492 patients were randomized to receive LONSURF in combination with bevacizumab (N=246) or LONSURF as a single agent (N=246). The trial population characteristics were as follows: median age 63 years, 52% male, 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown. 46% had ECOG PS 0 and 54% had ECOG PS 1. The primary site of disease was colon (73%) or rectum (27%). Seventy-one percent of patients had a RAS mutant status. A total of 92% of patients received 2 prior anticancer treatment regimens for advanced CRC; all patients received prior fluoropyrimidine; 99.8% of patients received prior irinotecan; 98% of patients received prior oxaliplatin. Among all 492 treated patients, 76% received prior anti-VEGF treatment, and 72% received an anti-VEGF monoclonal antibody. Among the 142 patients with RAS wild-type mCRC, 94% received prior anti-EGFR monoclonal antibody.</td>
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<td>Efficacy results are summarized in Table 9 and Figure 1.</td>
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<tr>
<th>201820, 02/10/2023</th>
<th>Tobramycin</th>
<th>Infectious Diseases</th>
<th>MT-RNR1</th>
<th>Warnings and Precautions</th>
<th>5 WARNINGS AND PRECAUTIONS</th>
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</thead>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>5.1 Ototoxicity</td>
</tr>
<tr>
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<td></td>
<td>Ototoxicity with use of BETHKIS</td>
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<tr>
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<td>Caution should be exercised when prescribing BETHKIS to patients with known or suspected auditory or vestibular dysfunction.</td>
</tr>
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<td>Findings related to ototoxicity as measured by audiometric evaluations and auditory adverse event reports were similar between BETHKIS and placebo in controlled clinical trials. Hearing loss was reported in two (1.1%) BETHKIS-treated patients and in one (0.9%) placebo-treated patient during clinical studies. Additionally, dizziness and vertigo, both of which may be manifestations of vestibular forms of ototoxicity, were observed in similar numbers of BETHKIS- and placebo-treated patients.</td>
</tr>
</tbody>
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<td>Tolterodine</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>018894</td>
<td>Tolazamide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<td>010670</td>
<td>Tolbutamide</td>
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<td>04/25/2023</td>
<td>Tofersen</td>
<td>Oncology</td>
<td>SOD1</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
<td>021228, 07/13/2018</td>
<td>Tolterodine</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<tbody>
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<td>FARESTON®</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td></td>
<td>Toremifene</td>
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<td>FARESTON® is an estrogen agonist/antagonist indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.</td>
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<tr>
<td>020497, 05/12/2017</td>
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<td>12.3 Pharmacokinetics</td>
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</tbody>
</table>
|                                     |           |                    |          |                  | Variability in Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6, the enzyme responsible for the formation of 5-HMT from tolterodine. The identified pathway of metabolism for these individuals (“poor metabolizers”) is dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as “extensive metabolizers.” Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HMT. Excretion: Following administration of a 5 mg oral dose of 14C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (< 2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (1% in poor metabolizers) was recovered as 5-HMT. A summary of mean (standard deviation) pharmacokinetic parameters of tolterodine extended release and 5-HMT in extensive (EM) and poor (PM) metabolizers is provided in Table 3. These data were obtained following single and multiple doses of tolterodine extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM). (See Table 3) (…)
|                                     |           |                    |          |                  | Drug Interactions: Potent CYP2D6 inhibitors: Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate release in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT, the pharmacologically active metabolite of tolterodine). Fluoxetine thus alters the pharmacokinetics in patients who could otherwise be CYP2D6 extensive metabolizers of tolterodine immediate release to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate release and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered. Potent CYP3A4 inhibitors: The effect of a 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were CYP2D6 poor metabolizers. In the presence of ketoconazole, the mean Cmax and AUC of tolterodine increased by 2- and 2.5 fold, respectively. Based on these findings, other potent CYP3A4 inhibitors may also lead to increases of tolterodine plasma concentrations. (…)
| 020281, 04/08/2019                   | Tramadol  | Anesthesiology     | CYP2D6  | Boxed Warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Patient Counseling Information | BOXED WARNING |
|                                     |           |                    | 1        |                  | ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN |
|                                     |           |                    |          |                  | Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in a t1 e a s t o n e case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). TRAMT is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of TRAMT in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol (see WARNINGS). |
|                                     |           |                    |          |                  | 5 WARNINGS AND PRECAUTIONS |
|                                     |           |                    |          |                  | 5.4 Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children |
|                                     |           |                    |          |                  | Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon post-marketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. |

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Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- ULTRAM is contraindicated for all children younger than 12 years of age (see Contraindications (4)).
- ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (see Contraindications (4)).
- Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hyperventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose (see Use in Specific Populations (8.4), Overdosage (10)).

**Nursing Mothers**

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethy tramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultrarapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking ULTRAM could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with ULTRAM (see Use in Specific Populations (8.2)).

**CYP2D6 Genetic Variability: Ultra-rapid metabolizer**

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1 or *1/*2). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-de methyl tramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see Overdosage (10)). Therefore, individuals who are ultra-rapid metabolizers should not use ULTRAM.

**8 USE IN SPECIFIC POPULATIONS**

**8.2 Lactation**

ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, O-desethyl-tramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or on the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding (see Clinical Pharmacology (12)). Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in the preterm, low birth-weight infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ULTRAM (see Warnings and Precautions (5.4), (5.7), (5.8), (10)).

**8.4 Pediatric Use**

The safety and effectiveness of ULTRAM in pediatric patients have not been established.

Life-threatening respiratory depression and death have occurred in children who received tramadol (see Warnings and Precautions (5.4)). In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

- ULTRAM is contraindicated for all children younger than 12 years of age (see Contraindications (4)).
- ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (see Contraindications (4)).
- Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hyperventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

**12 CLINICAL PHARMACOLOGY**

**12.3 Pharmacokinetics**

**Metabolism**

- Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are “poor metabolizers” of drugs such as debrisoquine, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower.

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204114, 06/22/2022
Trametinib (1) Oncology BRAF

The formation of the active metabolite, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower.

17 PATIENT COUNSELING INFORMATION

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise caregivers that ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 15 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 14 years of age receiving ULTRAM to monitor for signs of respiratory depression (see Warnings and Precautions (5.4)).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Melanoma
• Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST as a single agent or in combination with dabrafenib (see Clinical Studies (14.1), (14.2)).
• Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.
• Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib (see Clinical Studies (14.3)).
• Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.
• Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib (see Clinical Studies (14.4)).
• An FDA-approved test for the detection of BRAF V600E mutation in ATC is not currently available.
• Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib (see Clinical Studies (14.5)).
• An FDA-approved test for the detection of BRAF V600E mutation in solid tumors other than melanoma and NSCLC is not currently available.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Unresectable or Metastatic BRAF V600E Mutation Positive Melanoma
MEKINIST Administered as a Single Agent
Table 3 presents adverse reactions identified from analyses of the METRIC study, a randomized, open-label trial of patients with BRAF V600E or V600K mutation-positive melanoma receiving MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine 1,000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 every 3 weeks) (see Clinical Studies (14.1)).
Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma
The safety of MEKINIST when administered with dabrafenib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study (see Clinical Studies (14.2)).
Metastatic BRAF V600E Mutation-Positive NSCLC
The safety of MEKINIST when administered with dabrafenib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928).

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Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC)

The safety of MEKINIST when administered with dabrafenib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). [...] Advanced BRAF V600E-Mutation Positive Tumors

Study BRF117019

The safety of MEKINIST when administered with dabrafenib was evaluated in a multi-cohort, multi-center, non-randomized, open-label study in adult patients with cancers with the BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumor cohorts, and 65 in other malignancies [see Clinical Studies (14, 14.6)]. Patients received MEKINIST 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and effectiveness of MEKINIST in combination with dabrafenib in pediatric patients 6 years of age and older that weigh at least 26 kg was established based on data in adults and data from a pediatric study X2101. In study X2101, Parts C and D enrolled a total of 48 patients (ages 1 to 17) with the following tumor types: LGG (n = 34), HGG (n = 2), LCH (n = 11), and juvenile xanthogranulomatosis (n = 1) [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)]. The safety and effectiveness of MEKINIST in combination with dabrafenib in pediatric patients younger than 6 years old have not been established. The safety and effectiveness of MEKINIST as a single agent in pediatric patients have not been established.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

The pharmacokinetics (PK) of trametinib were characterized following single- and repeat-oral administration in patients with solid tumors and BRAF V600 mutation-positive metastatic melanoma. (…)

14 CLINICAL STUDIES

14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

Mekinist as a Single Agent

The safety and efficacy of MEKINIST were evaluated in an international, multicenter, randomized (2:1), open-label, active-controlled trial (Trial 1) in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. (…)

(…) Tumor tissue was evaluated for BRAF mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients (196 patients treated with MEKINIST and 93 chemotherapy-treated patients) were also tested retrospectively using an FDA-approved companion diagnostic test, THxID™-BRAF assay. (…)

(…) The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (less than 1%). The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for patients treated with MEKINIST and 3.1 months for patients treated with chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST. (…)

Mekinist with Dabrafenib

COMBI-d Study

The safety and efficacy of MEKINIST administered with dabrafenib were evaluated in an international, randomized, double-blind, active-controlled trial (the COMBI-d study; NCT01584648). The COMBI-d study compared dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment for patients with unresectable (Stage III) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive MEKINIST 2 mg once daily plus dabrafenib 150 mg twice daily or dabrafenib 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (greater than the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

In the COMBI-d study, 423 patients were randomized to MEKINIST plus dabrafenib (n = 211) or dabrafenib plus placebo (n = 212). The median age was 56 years (range: 22 to 89 years), 53% were male, >99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIc, 66% had M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing with the FDA-approved companion diagnostic test; 85% had BRAF V600E mutation-positive melanoma and 15% had BRAF V600K mutation-positive melanoma.

COMBI-MB Study

The activity of MEKINIST with dabrafenib for the treatment of BRAF V600E or V600K mutation-positive melanoma, metastatic to the brain, was evaluated in a non-randomized, open-label, multicenter, multi-cohort trial (the COMBI-MB study; NCT02039947). (…)

The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84 years), 58% were male, 100% were white, 8% were from the United States, 65% had a normal LDH value at baseline, and 97% had an ECOG performance status of 0 or 1. Intracranial metastases were asymptomatic in 87% and symptomatic in 13% of patients, 22% received prior loco-regional therapy for brain metastases, and 87% also had extracranial metastases. (…)

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<td>Oncology</td>
<td>G6PD</td>
<td>6 ADVERSE REACTIONS</td>
<td>6.1 Clinical Trials Experience</td>
</tr>
</tbody>
</table>
| **14.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma**

COMBI-AD (NCT01682083) was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations as detected by the Th12™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive MEKINIST 2 mg once daily in combination with dabrafenib 150 mg twice daily or two placebos for up to 1 year. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable brain metastases, distant metastatic disease, or prior systemic anticancer treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIa, IIb, or III). (...) In COMBI-AD, a total of 870 patients were randomized 438 to the MEKINIST in combination with dabrafenib and 432 to placebo. Median age was 51 years (range: 18 to 89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC stage IIB (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 13) (...) |

**14.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)**

In Study BRF139328 (NCT01336634), the safety and efficacy of dabrafenib alone or administered with MEKINIST were evaluated in a multicenter, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). (...) In a subgroup analysis of patients with retrospectively centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 14.|

**14.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer**

The safety and efficacy of MEKINIST administered with dabrafenib was evaluated in Study BRF117019 (NCT02034110), an activity-estimating, nine-cohort, multi-center, non-randomized, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. (...) |

**14.5 Lack of Clinical Activity in Metastatic Melanoma Following BRAF-Inhibitor Therapy**

The clinical activity of MEKINIST as a single agent was evaluated in a single-arm, multicenter, international trial in 40 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received MEKINIST at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity. The median age was 58 years, 63% were male, all were White, 98% had baseline ECOG PS of 0 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No patient achieved a confirmed partial or complete response as determined by the clinical investigators. |

**14.6 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors**

The safety and efficacy of MEKINIST in combination with dabrafenib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT212X2101, and supported by results in COMBI-d, COMBI-v (see Clinical Studies [14.2]), and BRF13928 [see Clinical Studies (14.4)]. In adult studies, patients received MEKINIST 2 mg once daily and dabrafenib 150 mg twice daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR). (BRF117019 Study and NCI-MATCH Study) Study BRF117019 (NCT02034110) [see Clinical Studies (14.5)] is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with the BRAF V600E mutation, including high grade glioma (HGG) (n = 45), biliary tract cancer (BTC) (n = 43), low grade glioma (LGG) (n = 13), adenocarcinoma of the colon (AOC) (n = 1), gastrointestinal stromal tumor (GIST) (n = 1), and anaplastic thyroid cancer (see Clinical Studies (14.5)). Patients were enrolled based on local assessments of BRAF V600E mutation status; a central laboratory confirmed the BRAF V600E mutation in 93 of 105 patients (91%). Arm A (EAY131-H) of the NCI-MATCH study included adult patients with solid tumors including gastrointestinal tumors (n = 14), lung tumors (n = 7), gynecologic or peritoneal tumors (n = 6), CNS tumors (n = 4), and ameloblastoma of mandible (n = 1). (...)

**14.7 BRAF V600E Mutation-Positive Metastatic Anaplastic Thyroid Cancer**

In Study BRF113928 (NCT01336634), the safety and efficacy of dabrafenib alone or administered with MEKINIST were evaluated in a multicenter, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). (...) In a subgroup analysis of patients with retrospectively centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 14.|

**14.8 Clinical Trials Experience**

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<tr>
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<th>G6PD</th>
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<td>(…) The trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVOT or RPED, QTcB interval ≥480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency. (…)</td>
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<td>RAS</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 New Primary Malignancies</td>
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<td>Non-Cutaneous Malignancies</td>
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<td>Based on its mechanism of action, dabrafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms; refer to the Prescribing Information for dabrafenib. Across clinical trials of MEKINIST administered with dabrafenib, non-cutaneous malignancies occurred in 1% of patients.</td>
</tr>
</tbody>
</table>

| 103792, 11/28/2018                     | Trastuzumab (1)       | Oncology          | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE |
|                                        |                       |                   |            | 1.1 Adjuvant Breast Cancer | |
|                                        |                       |                   |            | Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer | |
|                                        |                       |                   |            | as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel | |
|                                        |                       |                   |            | with docetaxel and carboplatin | |
|                                        |                       |                   |            | as a single agent following multi-modality anthracycline based therapy. | |
|                                        |                       |                   |            | 1.2 Metastatic Breast Cancer | |
|                                        |                       |                   |            | Herceptin is indicated: | |
|                                        |                       |                   |            | In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer | |
|                                        |                       |                   |            | As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. | |
|                                        |                       |                   |            | 1.3 Metastatic Gastric Cancer | |
|                                        |                       |                   |            | Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease. | |
|                                        |                       |                   |            | 2 DOSAGE AND ADMINISTRATION | |
|                                        |                       |                   |            | 2.1 Patient Selection | |
|                                        |                       |                   |            | Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics. | |
|                                        |                       |                   |            | Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. | |
|                                        |                       |                   |            | Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. | |
|                                        |                       |                   |            | 12 CLINICAL PHARMACOLOGY | |
|                                        |                       |                   |            | 12.2 Pharmacodynamics | |
|                                        |                       |                   |            | Cardiac Electrophysiology | |
|                                        |                       |                   |            | The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors. | |
|                                        |                       |                   |            | 14 CLINICAL STUDIES | |
|                                        |                       |                   |            | 14.1 Adjuvant Breast Cancer | |
|                                        |                       |                   |            | The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4). | |
|                                        |                       |                   |            | Studies 1 and 2 | |
|                                        |                       |                   |            | In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). (…) | |
|                                        |                       |                   |            | Study 3 | |
|                                        |                       |                   |            | In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. (…) | |
|                                        |                       |                   |            | (…) Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). (…) | |
|                                        |                       |                   |            | Study 4 | |
|                                        |                       |                   |            | In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. (…) | |
|                                        |                       |                   |            | (…) Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. | |

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<th>Labeling Text‡</th>
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<td>103792, 11/28/2018</td>
<td>Trastuzumab (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Adjuvant Breast Cancer Study 4</td>
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<td>† The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients &gt; 50 years of age (n = 1866), the OS hazard ratio was 0.83 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and/or PR-negative) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78) and in the subgroup of patients with hormone receptor-negative disease (ER-negative and/or PR-positive) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size &gt; 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80). (See Table 9). (…)</td>
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<td>761270, 11/01/2022</td>
<td>Tremelimumab-actl (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.2 Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>IMJUDO, in combination with durvalumab and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.</td>
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<td>14.2 Metastatic NSCLC</td>
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<td>Metastatic NSCLC - POSEIDON</td>
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<td>The efficacy of IMJUDO in combination with durvalumab and platinum-based chemotherapy in previously untreated metastatic NSCLC patients with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations was investigated in POSEIDON, a randomized, multicenter, active-controlled, open-label trial (NCT03164616), (…)</td>
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<td>Tremelimumab-actl (2)</td>
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<td>EGFR</td>
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<tr>
<td>761270, 11/01/2022</td>
<td>Tremelimumab-actl (3)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Metastatic NSCLC Metastatic NSCLC - POSEIDON The efficacy of IMJUDO in combination with durvalumab and platinum-based chemotherapy in previously untreated metastatic NSCLC patients with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations was investigated in POSEIDON, a randomized, multicenter, active-controlled, open-label trial (NCT03194616). Randomization was stratified by tumor cells (TC) PD-L1 expression (TC ≥ 50% vs. TC &lt; 50%), disease stage (Stage IVA vs. Stage IVB), and histology (non-squamous vs. squamous). A total of 675 patients were randomized to receive either IMJUDO with durvalumab and platinum-based chemotherapy (n=338) or platinum-based chemotherapy (n=337). The median age was 63 years (range: 27 to 87), 46% of patients age ≥ 65 years, 77% male, 57% White, 34% Asian, 0.3% Native Hawaiian or Other Pacific Islander, 3% American Indian or Alaska Native, 2% Black or African American, 4% Other Race, 79% former or current smoker, 34% ECOG PS 0, and 66% ECOG PS 1. Thirty-six percent had squamous histology, 63% non-squamous histology, 29% PD-L1 expression TC ≥ 50%, 71% PD-L1 expression TC &lt; 50%. (see Table 9).</td>
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<td>03/10/2022</td>
<td>Trofinetide</td>
<td>Psychiatry</td>
<td>PML-RARA</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Patient Counseling Information</td>
<td>1 INDICATIONS AND USAGE VESANOID is indicated for the induction of remission in adults and pediatric patients 1 year of age and older with acute promyelocytic leukemia (APL) characterized by the presence of the t(15;17) translocation or PML/RARα gene expression, and who are refractory to or who have relapsed from anthracycline chemotherapy or for whom anthracycline-based chemotherapy is contraindicated.</td>
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<tr>
<td>016792, 07/17/2014</td>
<td>Trimipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Drugs Metabolized by P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concommitant therapy.</td>
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<tr>
<td>213687, 06/30/2020</td>
<td>Triheptanoin</td>
<td>Inborn Errors of Metabolism</td>
<td>ACADVL, CPT2, HADHA, HADHB (Long-Chain Fatty Acid Oxidation Disorders)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE DGJULVI is indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD).</td>
</tr>
<tr>
<td>217026, 03/10/2023</td>
<td>Trofinetide</td>
<td>Neurology</td>
<td>MECP2</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES The efficacy of DAYBUE for the treatment of Rett syndrome was established in a 12-week randomized, double-blind, placebo-controlled study in patients with Rett syndrome 5 to 20 years of age (Study 1; NCT04181723). Patients (N=187) had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the MECP2 gene. Patients were randomized to receive DAYBUE (N=93) or matching placebo (N=94) for 12 weeks. The DAYBUE dosage was based on patient weight to achieve similar exposure in all patients [see Dosage and Administration (2.1)].</td>
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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</table>
| 213411, 01/19/2023                     | Tucatinib | Oncology          | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Metastatic Breast Cancer  
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.  
1.2 Unresectable or Metastatic Colorectal Cancer  
TUKYSA is indicated in combination with trastuzumab for the treatment of adult patients with RAS wild-type, HER2-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.  
2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Select patients for treatment of unresectable or metastatic colorectal cancer with TUKYSA based on the presence of:  
- HER2 overexpression or gene amplification [see Clinical Studies (14.2)], FDA-approved tests for the detection of HER2 overexpression and gene amplification in patients with unresectable or metastatic colorectal cancer are not currently available, and  
- RAS wild-type [see Clinical Studies (14.2)]. Information on FDA-approved tests for the detection of RAS mutations in patients with unresectable or metastatic colorectal cancer is available at http://www.fda.gov/CompanionDiagnostics.  
6 ADVERSE REACTIONS  
HER2-Positive Metastatic Breast Cancer  
(…) The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB [see Clinical Studies (14)]. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. (…) RAS Wild-Type, HER2-Positive Unresectable or Metastatic Colorectal Cancer  
The safety of TUKYSA in combination with trastuzumab or a non-US approved trastuzumab product was evaluated in 86 patients enrolled in MOUNTAINEER with unresectable or metastatic colorectal cancer [see Clinical Studies (14.2)]. The median duration of exposure to TUKYSA was 6.9 months (range 0.7, 49.3).  
14 CLINICAL STUDIES  
14.1 HER2-Positive Metastatic Breast Cancer  
The efficacy of TUKYSA in combination with trastuzumab and capecitabine was evaluated in 612 patients in HER2CLIMB (NCT02614794), a randomized (2:1), double-blind, placebo-controlled trial. Patients were required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases, and prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. HER2 positivity was based on archival or fresh tissue tested with an FDA-approved test at a central laboratory prior to enrollment [see Clinical Studies (14.2)]. TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of exposure was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. (…) RAS Wild-Type, HER2-Positive Metastatic Breast Cancer  
The efficacy of TUKYSA in combination with trastuzumab and capecitabine was evaluated in 84 patients enrolled in MOUNTAINEER (NCT0343313), an open-label, multicenter trial. Patients were required to have HER2-positive, RAS wild-type, unresectable or metastatic colorectal cancer and prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, and anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb). Patients whose disease had deficient mismatch repair (dMMR) proteins or microsatellite instability-high (MSI-H) must have also received an anti-programmed cell death protein-1 (PD-1) mAb. Patients who received prior anti-HER2 targeting therapy were excluded. HER2 positivity as defined by HER2 overexpression or gene amplification was prospectively determined in local laboratories using immunohistochemistry (IHC), in situ hybridization (ISH), and/or next generation sequencing (NGS) on tumor tissue. TUKYSA was performed as standard of care prior to study entry based expanded RAS testing including KRAS exons 2, 3, and 4 and NRAS exons 2, 3, and 4. (…)  
14.2 HER2-Positive Metastatic Colorectal Cancer  
The efficacy of TUKYSA in combination with trastuzumab was evaluated in 84 patients enrolled in MOUNTAINEER (NCT0343313), an open-label, multicenter trial. Patients were required to have HER2-positive, RAS wild-type, advanced unresectable or metastatic colorectal cancer and prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.2)]. TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of exposure was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. (…)  
2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Select patients for treatment of unresectable or metastatic colorectal cancer with TUKYSA based on the presence of:  
- RAS wild-type [see Clinical Studies (14.2)]. Information on FDA-approved tests for the detection of RAS mutations in patients with unresectable or metastatic colorectal cancer is available at http://www.fda.gov/CompanionDiagnostics.  
6 ADVERSE REACTIONS  
RAS Wild-Type, HER2-Positive Unresectable or Metastatic Colorectal Cancer  
The safety of TUKYSA in combination with trastuzumab or a non-US approved trastuzumab product was evaluated in 86 patients enrolled in MOUNTAINEER with unresectable or metastatic colorectal cancer [see Clinical Studies (14.2)]. The median duration of exposure to TUKYSA was 6.9 months (range 0.7, 49.3).  

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| 213411, 01/19/2023 | Tucatinib (3) | Oncology | RAS | Clinical Studies | 14 CLINICAL STUDIES  
14.2 HER2-Positive Metastatic Colorectal Cancer  
The efficacy of TUKYSA in combination with trastuzumab was evaluated in 84 patients in MOUNTAINEER (NCT03043313), an open-label, multicenter trial. Patients were required to have HER2-positive, RAS wildtype, unselectable or metastatic colorectal cancer and prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, and anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb). Patients whose disease had deficient mismatch repair (dMMR) proteins or microsatellite instability-high (MSI-H) must have also received an anti-programmed cell death protein-1 (PD-1) mAb. Patients who received prior anti-HER2 targeting therapy were excluded. HER2 positivity as defined by HER2 overexpression or gene amplification was prospectively determined in local laboratories using immunohistochemistry (IHC), in situ hybridization (ISH), and/or next generation sequencing (NGS) on tumor tissue. RAS status was performed as standard of care prior to study entry based on expanded RAS testing including KRAS exons 2, 3, and 4 and NRAS exons 2, 3, and 4. (…)|
| 205382, 05/11/2022 | Umeclidinium | Pulmonary | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Umeclidinium and Cytochrome P450 2D6:  
In vitro metabolism of umclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing to normal (ultrarapid, extensive, and intermediate metabolizers) and CYP2D6 poor metabolizer subjects (Figure 1). |
| 211675, 08/16/2019 | Upadacitinib | Rheumatology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Drug Interaction Studies  
Potential for Other Drugs to Influence the Pharmacokinetics of Upadacitinib  
Upadacitinib is metabolized in vitro by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 3 [see Drug Interactions (7)]. pH modifying medications (e.g., antacids or proton pump inhibitors) are not expected to affect upadacitinib plasma exposures based on in vitro assessments and population pharmacokinetic analyses. CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics (based on population pharmacokinetic analyses), indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures. |
| 761044, 09/23/2016 | Ustekinumab | Dermatology, Gastroenterology | IL12A, IL12B, IL23A | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.2 Theoretical Risk for Vulnerability to Particular Infections  
Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonellae (including nontyphoid strains), and Bacillus Calmette-Guérin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances. |
| 209241, 08/18/2023 | Valbenazine | Neurology | CYP2D6 | Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS  
5.4 QT Prolongation  
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP34A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant [see Clinical Pharmacology (12.2)]. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dosage reduction may be necessary. For patients taking a strong CYP34A4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily [see Dosage and Administration (2.3, 2.4)]. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.  
8 USE IN SPECIFIC POPULATIONS  
8.6 CYP2D6 Poor Metabolizers  
Dosage reduction of INGREZZA is recommended for known CYP2D6 poor metabolizers [see Dosage and Administration (2.3)]. Increased exposure (Cmax and AUC) to valbenazine’s active metabolite was observed in CYP2D6 poor metabolizers. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions [see Clinical Pharmacology (12.3, 12.4)]. |

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<td>018081, 02/21/2019</td>
<td>Valproic Acid (1)</td>
<td>Neurology</td>
<td>POLG</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
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<tr>
<td>018081, 02/21/2019</td>
<td>Valproic Acid (2)</td>
<td>Neurology</td>
<td>Nonspecific (Urea Cycle Disorders)</td>
<td>Contraindications, Warnings and Precautions</td>
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### 12 CLINICAL PHARMACOLOGY

#### 12.2 Pharmacodymanic

**Cardiac Electrophysiology**

(*…*) INGREZZA may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking INGREZZA 60 mg or 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean (upper bound of double-sided 90% CI) QT prolongation of 9.6 (12.0) msec or 11.7 (14.7) msec, respectively, as compared to otherwise healthy volunteers given INGREZZA, who had a respective mean (upper bound of double-sided 90% CI) QT prolongation of 5.3 (6.7) msec or 6.7 (8.4) msec [see Warnings and Precautions (5.4)]

#### 12.5 Pharmacogenomics

CYP2D6 metabolizes the active metabolite of valbenazine ([+]H-TBZ). The gene encoding CYP2D6 has polymorphisms that impact protein function. CYP2D6 poor metabolizers are individuals with two nonfunctioning alleles, resulting in no enzyme activity.

Pharmacokinetic data from CYP2D6 poor metabolizers (n=25) treated with valbenazine demonstrate an approximate 2-fold higher AUCinf and a 1.6-fold higher Cmax, of ([+]H-TBZ) compared to normal metabolizers. Dosage reduction is recommended in CYP2D6 poor metabolizers [see Dosage and Administration (2.3), Warnings and Precautions (5.5), and Use in Specific Populations (8.6)].

In a clinical study, AUC of ([+]H-TBZ) was 22% higher and Cmax was 9% lower in intermediate metabolizers (n=7) as compared to normal metabolizers (n=11), which is not considered clinically relevant. The effects of ultra rapid metabolizer status on the pharmacokinetics of ([+]H-TBZ) have not been studied. Approximately 7% of White populations, 2% of Asian populations, and 2% of African-American populations are poor metabolizers.

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| 202429, 05/18/2020                     | Vemurafenib (1) | Oncology | BRAF | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information | 1 INDICATIONS AND USAGE
1.1 Unresectable or Metastatic Melanoma
ZELBORAF® is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].

1.2 Erdheim-Chester Disease
ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Confirm the presence of BRAF V600E mutation in melanoma tumor specimens prior to initiation of treatment with ZELBORAF [see Warnings and Precautions (5.2)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at http://www.fda.gov/CompanionDiagnostics.

5 WARNINGS AND PRECAUTIONS
5.2 Tumor Promotion in BRAF Wild-Type Melanoma
In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation in tumor specimens prior to initiation of ZELBORAF [see Indications and Usage (1) and Dosage and Administration (2.1)]

5.5 QT Prolongation
Concentration-dependent QT prolongation occurred in an uncontrolled, open-label QT sub-study in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [see Clinical Pharmacology (12.2)]. (…)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(….) Unresectable or Metastatic Melanoma with BRAF V600E Mutation
This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 [see Clinical Studies (14)]. (…)

Erdheim-Chester Disease (ECD)
This section describes adverse reactions identified from analyses of Trial 4 [see Clinical Studies (14)]. In Trial 4, 22 patients with BRAF V600 mutation-positive ECD received ZELBORAF 960 mg twice daily.

The median treatment duration for ECD patients in this study was 14.2 months. Table 3 presents adverse reactions reported in at least 20% of BRAF V600 mutation-positive ECD patients treated with ZELBORAF.

In Trial 4, the most commonly reported adverse reactions (≥ 50%) in patients with BRAF V600 mutation-positive ECD treated with ZELBORAF were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The most common (≥ 10%) Grade 3 adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculo-papular, and arthralgia. (…)

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of ZELBORAF in pediatric patients have not been established. Vemurafenib was studied in 6 adolescent patients 15 to 17 years of age with unresectable or metastatic melanoma with BRAF V600 mutation. A maximum tolerated dose was not reached with doses up to vemurafenib 960 mg twice daily. No new safety signals were observed. Vemurafenib steady-state exposure in these 6 adolescent patients was generally similar to that in adults.

12 CLINICAL PHARMACOLOGY

* Therapeutic areas do not necessarily reflect the CDER review division.
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### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
</tr>
</thead>
</table>
| 12/19/2017 | Venlafaxine | Psychiatry | CYP2D6 | 7 DRUG INTERACTIONS | 7.5 Weight Loss Agents
The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. (See Figure 1) |
| 020699, 12/19/2017 | Venlafaxine | Psychiatry | CYP2D6 | 7 DRUG INTERACTIONS | 7 USE IN SPECIFIC POPULATIONS
8.6 Age and Gender
A population pharmacokinetic analysis of 404 Effexor-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary [see Dosage and Administration (2.6)] (see Table 15). (See Figure 3) |
| 020429, 05/18/2020 | Vemurafenib (2) | Oncology | RAS | 5 WARNINGS AND PRECAUTIONS | Other Malignancies
Based on mechanism of action, ZELBORAF may promote malignancies associated with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies. |

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</table>
| 208573, 05/29/2020 | Venetoclax (1) | Oncology | Chromosome 17p | Clinical Studies | 14 CLINICAL STUDIES
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Combination Therapy

**Clinical Studies**

**CLL14**

(…)

A total of 432 patients were randomized, 216 to each study arm. Baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, 6% were male; 36% and 43% were Binet stage B and C, respectively, and 88% had Eastern Cooperative Oncology Group (ECOG) performance status <2. The median CR53 score was 8.6 (range: 0 to 28) and 58% of patients had CLcr <70 mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 10%, 11q deletion in 19%, and unmutated IgVH in 19%. (…)

**MURANO**

(…)

Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (See Table 21) (…) Monotherapy

The efficacy of VENCLEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies.

**Study M13-982**

The efficacy of VENCLEXTA was established in study M13-982 (NCT01889186), an open-label, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vyvis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. (See Table 23) (…)

**Study M12-175**

Study M12-175 (NCT01328626) was a multicenter, open-label trial that enrolled previously treated patients with CLL or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients (69 with CLL, 8 with SLL) who had received a 400 mg daily dose of VENCLEXTA. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months).

The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥25 cm, 30% of patients had ALC ≥25 x 10^9 /L, 33% had documented unmutated IgVH. (…)

Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≥25 cm, 31% had an absolute lymphocyte count ≥25 x 10^9 /L, 57% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)

| 208573, 05/29/2020 | Venetoclax (2) | Oncology | Chromosome 11q | Clinical Studies | 14 CLINICAL STUDIES
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Combination Therapy

**Clinical Studies**

**CLL15**

(…)

Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…)

**MURANO**

(…)

Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…)

| 208573, 05/29/2020 | Venetoclax (3) | Oncology | TP53 | Clinical Studies | 14 CLINICAL STUDIES
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Combination Therapy

**Clinical Studies**

**CLL14**

(…)

The median CR53 score was 8.0 (range: 0 to 28) and 58% of patients had CLcr<70 mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmutated IgVH in 57%. (…)

**MURANO**

(…)

Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…)

**Study M14-358**

**14.2 Acute Myeloid Leukemia**

**Combination Therapy**

**VENCLEXTA**

in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…)

Study M14-387

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<td>Venetoclax (4) Oncology</td>
<td>IDH1</td>
<td>14 CLINICAL STUDIES</td>
<td>14.2 Acute Myeloid Leukemia Study M14-358</td>
<td>VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)</td>
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<td>Venetoclax (5) Oncology</td>
<td>IDH2</td>
<td>14 CLINICAL STUDIES</td>
<td>14.2 Acute Myeloid Leukemia Study M14-358</td>
<td>VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)</td>
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<td>IGHV</td>
<td>14 CLINICAL STUDIES</td>
<td>14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy ClL14</td>
<td>(…) The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLc&lt;70mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmutated IgVH in 57%. (…) MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…) Study M12-175 (…) The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 15). At baseline, 67% of patients had one or more nodes ≤5 cm, 30% of patients had ALC ≥25 x 109 /L, 33% had documented unmutated IgVH, and 21% had documented 17p deletion. (…) Study M14-032 (…) Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≤5 cm, 31% had an absolute lymphocyte count ≥25 x 109 /L, 57% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)</td>
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<td>NPM1</td>
<td>14 CLINICAL STUDIES</td>
<td>14.2 Acute Myeloid Leukemia Study M14-358</td>
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<td>FLT3</td>
<td>14 CLINICAL STUDIES</td>
<td>14.2 Acute Myeloid Leukemia Study M14-358</td>
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</table>
| 04/02/2021, 212154, 04/02/2021, 211964 | Viltolarsen | Neurology | DMD | Clinical Pharmacology | Viltolarsen was studied in a non-randomized, open-label clinical trial (NCT02203773) of VILEXCTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…)

(…) Patients initiated VILEXCTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-grade cytarabine was not implemented in the clinical trial. (See Table 26) (…)

| 04/02/2021, 211964 | Viltolarsen | Psychiatry | CYP2D6 | Clinical Pharmacology | A multiple-dose study was conducted with Qelbree 900 mg once-daily in healthy volunteers to compare the effect of CYP2D6 poor metabolizers (PMs) and extensive metabolizers (EMs) on the PK of viltolarsen. At steady state, viltolarsen geometric means for Cmax and AUC0-24 were 21% and 26%, respectively, higher in CYP2D6 EMs compared to PMs.

| 04/02/2021, 211964 | Viltolarsen | Psychiatry | SLC01B1 | Clinical Pharmacology | In Vitro Studies

Based on in vitro data, drugs that inhibit CYP isozymes 1A1, 1A2, 2B6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of viltolarsen.

Viltolarsen does not inhibit CYP2C8, 2C9 or 2C19 activities. Viltolarsen is a reversible inhibitor of CYP2A6 and CYP2B6. Viltolarsen is not a inhibitor of P-gp, BCRP, MATE2-K, OATP1B1*1a, and OATP1B3 transporters. Viltolarsen appears to be a weak inhibitor of the MATE1. Viltolarsen is not a substrate of either OATP1B1*1a or OATP1B3 transporters.

| 212154, 08/12/2020 | Viltolarsen | Neurology | DMD | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE

VILEXCTA is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VILEXCTA [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In clinical trials with VILEXCTA, 32 patients have been exposed to VILEXCTA once weekly, ranging between 40 mg/kg (0.5 times the recommended dosage) and 80 mg/kg (the recommended dosage), including 16 patients treated for greater than 12 months and 8 patients treated for greater than 24 months as part of an ongoing open-label extension study. All patients were male and had genetically confirmed DMD. (…)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

VILEXCTA is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping, including pediatric patients [see Clinical Studies (14)].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The pharmacokinetics of viltolarsen were evaluated in DMD patients following administration of intravenous (IV) doses ranging from 1.25 mg/kg/week (0.016 times the recommended dosage) to 80 mg/kg/week (the recommended dosage). Viltolarsen exposure increased proportionally with dose, with minimal accumulation with once-weekly dosing. Inter-subject variability (as %CV) for Cmax and AUC ranged from 16% to 27% respectively. VILEXCTA is administered as an IV infusion over 60 minutes. Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion).

Specific Populations

Age, Sex & Race

The pharmacokinetics of viltolarsen have been evaluated only in male pediatric DMD patients. There is no experience with VILEXCTA in patients 65 years of age or older. No marked differences in any PK parameters were observed between White and Asian patients.

Patients with Renal or Hepatic Impairment

VILEXCTA has not been studied in patients with renal or hepatic impairment. Viltolarsen was found to be metabolically stable, and hepatic metabolism does not contribute to the elimination of viltolarsen. In addition, viltolarsen was mainly excreted unchanged in the urine. Viltolarsen is eliminated renally, and renal impairment is expected to result in increasing exposure of viltolarsen. However, because of the effect of reduced skeletal muscle mass on creatinine measurements in DMD patients, no specific dosage adjustment can be recommended for DMD patients with renal impairment based on glomerular filtration rate estimated by serum creatinine [see Use in Specific Populations (8.6)].

14 CLINICAL STUDIES

The effect of VILEXCTA on dystrophin production was evaluated in one study in DMD patients with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping (Study 1; NCT02740972). (…)
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| Vincristine | Oncology          | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Adult ALL in Second or Greater Relapse  
Marqibo is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified.  
 6 ADVERSE REACTIONS  
Acute Lymphoblastic Leukemia Relapsed or Refractory Philadelphia Chromosome Negative ALL  
The safety of Marqibo was evaluated in a total of 83 adults in two trials: study 1 and study 2. Patients received Marqibo 2.25 mg/m² once every seven days. Adverse reactions were observed in 100% of patients. The most common adverse reactions (>30%) were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%).  
 14 CLINICAL STUDIES  
14.1 Acute Lymphoblastic Leukemia  
Marqibo was studied in an international, open-label, multi-center, single-arm trial (Study 1). Eligible patients were 18 years of age or older with Philadelphia chromosome negative ALL in second or greater relapse or whose disease progressed after two or greater treatment lines of anti-leukemia therapy. Patients had to have achieved a complete remission (CR) at least one prior anti-leukemia chemotherapy, defined by a leukemia-free interval of equal or more than 90 days. Patients were eligible for immediate hematopoietic stem cell transplantation (HSCT) at the time of screening and enrollment. (...) |
| Voriconazole | Infectious Diseases | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Metabolism  
In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP3A4, CYP2C19 and CYP3A4 [see Drug Interactions (7)]. In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCt) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts. (...)  
12.5 Pharmacogenomics  
CYP2C19, significantly involved in the metabolism of voriconazole, exhibits genetic polymorphism. Approximately 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCt) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts [see Clinical Pharmacology (12.3)]. |
| Vortioxetine | Psychiatry | CYP2D6 | Dosage and Administration, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION  
2.6 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors  
The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued [see Drug Interactions (7.3)]. |
| Voxelotor | Hematology | HBB | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Metabolism and Elimination  
Voxelotor is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronide acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of voxelotor to its major pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the voxelotor plasma concentration of extensive metabolizers. (...) |
| Vutrisiran | Neurology | TTR | Adverse Reactions, Clinical Studies | 6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience |
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<td>009218, 08/14/2017</td>
<td>Warfarin (1)</td>
<td>Hematology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Drug Interactions, Clinical Pharmacology</td>
<td>The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by: • Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities • Genetic factors (CYP2C9 and VKORC1 genotypes) [see Clinical Pharmacology (12.5)] (…) Dosing Recommendations without Consideration of Genotype If the patient’s CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg once daily. Determine each patient’s dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily. Dosing Recommendations with Consideration of Genotype Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see Clinical Pharmacology (12.5)]. If the patient’s CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*1, *2/*2, *2/*3, and *3/*3 may require more prolonged time (&gt;2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants. (See Table 1)</td>
</tr>
<tr>
<td>009218, 08/14/2017</td>
<td>Warfarin (2)</td>
<td>Hematology</td>
<td>VKORC1</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by: • Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities • Genetic factors (CYP2C9 and VKORC1 genotypes) [see Clinical Pharmacology (12.5)] (…) Dosing Recommendations without Consideration of Genotype If the patient’s CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg once daily. Determine each patient’s dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily. Dosing Recommendations with Consideration of Genotype</td>
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</table>

* Therapeutic areas do not necessarily reflect the CDER review division.
† Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.
‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.
Blue text represents the most recent additions and/or changes since last posted version.
Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see Clinical Pharmacology (12.5)]. If the patient’s CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*1, *2/*2, *3/*3, and *3/*3 may require a longer dosing interval to achieve target INR. (See Table 1)

### 5 WARNINGS AND PRECAUTIONS

#### 5.8 Other Clinical Settings with Increased Risks

**In the following clinical settings, the risks of COUMADIN therapy may be increased:**

(…)

Deficiency in protein C-mediated anticoagulant response: COUMADIN reduces the synthesis of the naturally occurring anticoagulants, protein C and protein S. Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimize the incidence of tissue necrosis in these patients. (…)

### 12 CLINICAL PHARMACOLOGY

#### 12.5 Pharmacogenomics

CYP2C9 and VKORC1 Polymorphisms

The S-enantiomer of warfarin is mainly metabolized to 7-hydroxycoumarin by CYP2C9, a polymorphic enzyme. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased expression levels of the S-warfarin, which is metabolized by CYP2C9. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. In other populations, including non-Caucasian populations, the frequencies of these alleles range from 0% to 5% for CYP2C9*2 and 3% to 8% for CYP2C9*3.

#### 12.6 Pharmacodynamics

Warfarin is a vitamin K antagonist that irreversibly inhibits factor VIIa and factor Xa, and inactivates factors II, VII, IX, and X for 1 to 2 days. The plasma concentrations of the affected vitamin K-dependent clotting factors and anticoagulation proteins are typically maintained for 2 to 5 days after a single dose of warfarin. The peak anticoagulant effect typically occurs 12 to 48 hours after a single dose of warfarin, and the duration of action of a single dose of warfarin is 2 to 5 days. The effects of COUMADIN may become more pronounced as effects of daily maintenance doses overlap. This is consistent with the half-lives of the affected vitamin K-dependent clotting factors and anticoagulation proteins: Factor II - 60 hours, VII - 4 to 6 hours, IX - 24 hours, X - 48 to 72 hours, and proteins C and S are approximately 8 hours and 30 hours, respectively.

### 14 CLINICAL STUDIES

#### 14.2 Waldenström’s Macroglobulinemia

The efficacy of BRUKINSA was evaluated in ASPEN [NCT0353440], a randomized, active control, open-label trial, comparing BRUKINSA and ibritumomab in patients with MYD88 L265P mutation (MYD88MUT) WM. Patients in Cohort 1 (n=201) were randomized 1:1 to receive BRUKINSA 160 mg twice daily or rituximab 420 mg once daily until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (0 versus 1-3 versus > 3) and CXCRII status (presence or absence of a WHIM-like mutation as measured by Sanger assay). ASPEN Cohort 2 Cohort 2 enrolled patients with MYD88 wildtype (MYD88WT) or MYD88 mutation unknown WM and received BRUKINSA 160 mg twice daily. The median age was 72 years (range: 39 to 87) with 43% ≥ 75 years, 50% were male, 96% were White and 4% were not reported (unknown race). 86% of patients had a baseline ECOG performance status 0 or 1 and 14% had a baseline performance status of 2. Twenty-three of the 28 patients in Cohort 2 had
Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 12/2023

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>213217, 04/21/2023</td>
<td>Zanubrutinib (2)</td>
<td>Oncology</td>
<td>Chromosome 1p</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>Single-arm cohort: Previously untreated CLL/SLL and 17p deletion</td>
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<td>In 111 patients with previously untreated, 17p del CLL/SLL, the median age was 70, 71% were male, 95% were White, and 1% were Asian. Most patients (87%) had an ECOG performance status of 0 to 1. The median duration of exposure to BRUKINSA was 30 months. (See Tables 11 and 12)</td>
</tr>
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</table>

### 14 CLINICAL STUDIES

14.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The efficacy of BRUKINSA in patients with CLL/SLL was evaluated in two randomized controlled trials.

**SEQUOIA**

(…) Additionally, the same BRUKINSA regimen was evaluated in 110 patients with previously untreated, 17p del CLL/SLL in a non-randomized cohort. Efficacy is summarized according to cohort.

**ALPINE**

The trial enrolled 652 patients with relapsed or refractory CLL/SLL after at least 1 systemic therapy. The patients were randomized in a 1:1 ratio to receive either BRUKINSA 160 mg orally twice daily (n=327) or brutinib 420 mg orally once daily (n=325), each administered until disease progression or unacceptable toxicity. Randomization was stratified by age, geographic region, refractoriness to last therapy, and 17p deletion/TP53 mutation status. Baseline characteristics were generally similar between treatment arms. Efficacy was based on overall response rate and duration of response as assessed by an IRC. Efficacy results are presented in Table 20 and Figure 1. At the time of analysis, overall survival data were immature. With an estimated median followup of 25.7 months, median overall survival was not reached in either arm, with fewer than 7% of patients experiencing an event. Single-arm cohort: Previously untreated CLL/SLL with 17p deletion

In this cohort, 110 patients with previously untreated CLL/SLL and centrally confirmed 17p deletion received BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity. The median age was 70, 71% were male, 95% were White, and 1% were Asian. Sixty percent of patients had an unmutated IGHV gene and 36% had Binet Stage C disease. Efficacy was based on overall response rate and duration of response as assessed by an IRC. Efficacy results are presented in Table 21.

**ALPINE**

The efficacy of BRUKINSA in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE, a randomized, multicenter, open-label, actively controlled trial (NCT03734016). The trial enrolled 652 patients with relapsed or refractory CLL/SLL after at least 1 systemic therapy. The patients were randomized in a 1:1 ratio to receive either BRUKINSA 160 mg orally twice daily (n=327) or brutinib 420 mg orally once daily (n=325), each administered until disease progression or unacceptable toxicity. Randomization was stratified by age, geographic region, refractoriness to last therapy, and 17p deletion/TP53 mutation status. Baseline characteristics were similar between treatment arms. Overall, the median age was 67 years, 68% were male, 81% were White, 14% were Asian, 1% were Black. Forty-three percent had advanced stage disease, 73% had an unmutated IGHV gene, and 23% had 17p deletion or TP53 mutation. Patients had a median of one prior line of therapy (range: 1-8), 18% of patients had ≥3 prior lines of therapy, 78% had prior chemotherapy, and 2.3% had prior BCL2 inhibitor. Efficacy was based on overall response rate and duration of response as determined by an IRC. Efficacy results are shown in Table 22. At the time of analysis, overall survival data were immature. With an estimated median followup of 24.7 months, median overall survival was not reached in either arm with 11% of patients experiencing an event.

**14.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma**

The efficacy of BRUKINSA in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE, a randomized, multicenter, open-label, actively controlled trial (NCT03734016). The trial enrolled 652 patients with relapsed or refractory CLL/SLL after at least 1 systemic therapy. The patients were randomized in a 1:1 ratio to receive either BRUKINSA 160 mg orally twice daily (n=327) or brutinib 420 mg orally once daily (n=325), each administered until disease progression or unacceptable toxicity. Randomization was stratified by age, geographic region, refractoriness to last therapy, and 17p deletion/TP53 mutation status. Baseline characteristics were similar between treatment arms. Overall, the median age was 67 years, 68% were male, 81% were White, 14% were Asian, 1% were Black. Forty-three percent had advanced stage disease, 73% had an unmutated IGHV gene, and 23% had 17p deletion or TP53 mutation. Patients had a median of one prior line of therapy (range: 1-8), 18% of patients had ≥3 prior lines of therapy, 78% had prior chemotherapy, and 2.3% had prior BCL2 inhibitor. Efficacy was based on overall response rate and duration of response as determined by an IRC. Efficacy results are shown in Table 22. At the time of analysis, overall survival data were immature. With an estimated median followup of 24.7 months, median overall survival was not reached in either arm with 11% of patients experiencing an event.

### 6 ADVERSE REACTIONS

Efficacy results are presented in Table 22. At the time of analysis, overall survival data were immature. With an estimated median followup of 24.7 months, median overall survival was not reached in either arm with 11% of patients experiencing an event.

**216834, 10/17/2023**

Zilucoplan | Neurology | ACHR | Indications and Usage, Clinical Studies | **1 INDICATIONS AND USAGE**

ZILBRYSO is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (ACHR) antibody positive.

**14 CLINICAL STUDIES**

The efficacy of ZILBRYSO for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-AChR antibody positive was established in a 12-week, multicenter, randomized, double-blind placebo-controlled study (Study 1; NCT04115293).

Study 1 enrolled patients who met the following criteria:...
### Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 12/2023

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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, • Positive serology for AChR binding autoantibodies, • MG-Activities of Daily Living (MG-ADL) total score of ≥6, • Those on MG therapy prior to screening (including acetylcholinesterase (AChE) inhibitors, steroids, or non-steroidal immunosuppressive therapies (NSISTs), either in combination or alone), needed to maintain a stable dose. […]</td>
<td></td>
<td></td>
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