Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 12/2020

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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</tr>
</thead>
</table>
| 020977, 03/20/2017                     | Abacavir | Infectious Diseases | HLA-B | Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions | BOXED WARNING
WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

Hypersensitivity Reactions
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.
• If a hypersensitivity reaction is ruled out, patients may restart ZIAGEN. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of restarting abacavir therapy. Therefore, reintroduction of ZIAGEN or any other abacavir containing product is recommended only if medical care can be readily accessed.
• A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refills.

208716, 03/30/2020 Abemaciclib (1) Oncology ESR (Hormone Receptor) Indications and Usage, Adverse 1 INDICATIONS AND USAGE VERZENIO™ (abemaciclib) is indicated:

* 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>
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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>208716, 03/30/2020</td>
<td>Abemaciclib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>VERZENIO™ (abemaciclib) is indicated:</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>• 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.</td>
</tr>
</tbody>
</table>

### 6 ADVERSE REACTIONS

#### 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. (…)

**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. (…)

**VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)**

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

**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)**

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

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with endocrine therapy who had not received chemotherapy in the metastatic setting. (…)

**VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)**

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

MONARCH 1 (NCT02102490) was 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. (…)

### 1 INDICATIONS AND USAGE

**VERZENIO™ (abemaciclib) is indicated:**

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women 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 women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- 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

**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. (…)

### Table of Pharmacogenomic Biomarkers in Drug Labeling

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient Population</th>
<th>Biomarker(s)</th>
<th>Labeling Text</th>
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<tbody>
<tr>
<td><strong>MONARCH 3</strong></td>
<td><strong>VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole)</strong></td>
<td><strong>HER2</strong></td>
<td><strong>Nonspecific</strong> 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.</td>
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<td>Biomarker†</td>
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<td>Ado-Trastuzumab Emtansine</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
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<th>Labeling Text‡</th>
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<td>201292, 10/11/2019</td>
<td>Afatinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>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 KADYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADYLA-treated group and 5.5 months for patients treated with lapatinib and capecitabine, respectively. (...) Early Breast Cancer KADYLA 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 KADYLA or trastuzumab. The median duration of study treatment was 10 months for patients in the KADYLA-treated group and 10 months for patients treated with trastuzumab. (...) 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Cardiac Electrophysiology The effect of multiple doses of KADYLA (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., &gt; 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 KADYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=15), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment. (...) 14 CLINICAL STUDIES 14.1 Metastatic Breast Cancer The efficacy of KADYLA 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 1486 patients with HER2-positive, early breast cancer. Patients were required to have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. Patients received radiation therapy 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 KADYLA 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. KADYLA 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 KADYLA 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 KADYLA- and trastuzumab-treated patients. Patients who discontinued KADYLA 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; 94% of these patients received pertuzumab. (...) 14.3 HER2-Positive Early Breast Cancer Pertuzumab was approved for patients with HER2-positive early breast cancer who have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. Patients were randomized (1:1) to receive KADYLA or trastuzumab plus pertuzumab. 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. KADYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADYLA 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 17.8 months for both KADYLA- and trastuzumab-treated patients. Patients who discontinued KADYLA 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 (75%) 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; 94% of these patients received pertuzumab. (...) 14.4 HER2-Positive Early Breast Cancer Trastuzumab was approved for patients with HER2-positive early breast cancer who have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. Patients were randomized (1:1) to receive KADYLA or trastuzumab plus 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. KADYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADYLA 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 17.8 months for both KADYLA- and trastuzumab-treated patients. Patients who discontinued KADYLA 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 (81%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. 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<tbody>
<tr>
<td>208434, 06/05/2018</td>
<td>Alectinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>(…) The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naive, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled 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 trial assay (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 RQ PCR Kit, which is FDA-approved for selection of patients for GILOTRIF treatment. Among the patients randomized, 65% were female, median age was 61 years, baseline EOGO 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 (S768I, 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 [NCT01121393]). • LUX-Lung 2 was a single arm, multicenter study of alectinib 40 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 3 was a randomized, multicenter study comparing treatment with alectinib 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 RQ PCR Kit. • LUX-Lung 6 was a randomized, multicenter study comparing treatment with alectinib 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 75 GILOTRIF treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. Among the 32 patients with a confirmed non-resistant EGFR mutation, the median age was 60.5 years (range 32-79), 60% were female, 97% were Asian, 3% were other races, 38% had an ECOG PS of 0, 63% had an ECOG PS 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIb 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. Overall Survival Rates in Other EGFR Mutations The number of patients, the number of responders, and durations of response in subgroups are provided in Table 7. The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (S768I, 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 [NCT01121393]). • LUX-Lung 2 was a single arm, multicenter study of alectinib 40 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 3 was a randomized, multicenter study comparing treatment with alectinib 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 RQ PCR Kit. • LUX-Lung 6 was a randomized, multicenter study comparing treatment with alectinib 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 75 GILOTRIF treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. 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---|---|---|---|---|---
| | | | | | 

- **Table of Pharmacogenomic Biomarkers in Drug Labeling**

**Therapeutic Areas**

- **Oncology**
- **Inborn Errors of Metabolism**
- **Others**

**Biomarkers**

- **ERBB2 (HER2)**
- **PIK3CA**

**Labeling Text**

- Alectinib reached maximal concentrations at 4 hours following administration of ALECENSA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC. (…)
- Distribution
  - The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4.
  - Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration.
- Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma. (…)
- Elimination
  - The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC.

### 14 CLINICAL STUDIES

**Previously Untreated ALK-Positive Metastatic NSCLC**

The efficacy of ALECENSA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ALEX: NCT01075840). 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. (…)

ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib

The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials: NPS28671 (NCT01588028) and NPS28673 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. (…)

**5 WARNINGS AND PRECAUTIONS**

- **5.2 Immune-Mediated Reactions**
  - Immune-mediated cutaneous reactions have been reported with alectinib including necrotizing skin lesions [see Adverse Reactions (6.3)]. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alectinib and alglucosidase alfa. These reactions occurred several weeks to 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 alectinib or alglucosidase alfa should undergo periodic urinalysis [see Adverse Reactions (6.3)]. (…)

### 14 CLINICAL STUDIES

**Previously Untreated ALK-Positive Metastatic NSCLC**

The efficacy of ALECENSA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ALEX: NCT01075840). 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. (…)

ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib

The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials: NPS28671 (NCT01588028) and NPS28673 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. (…)

**5.5 Risk of Antibody Development**

Patients with infantile-onset Pompe disease should have a cross-reactive immunologic material (CRIM) assessment early in their disease course and be managed by a clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. Immune tolerance induction administered prior to and in conjunction with initiation of alglucosidase alfa has been reported to aide tolerability of alglucosidase alfa in CRIM-negative patients. CRIM status has been shown to be associated with immunogenicity and patients' responses to enzyme replacement therapies. CRIM-negative infants with infantile-onset Pompe disease treated with alglucosidase alfa have shown slower clinical response in the presence of high sustained IgG antibody titers and positive inhibitory antibodies compared to CRIM-positive infants [see Adverse Reactions (6.2)]. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained IgG antibody titers, including CRIM-negative patients (i.e., patients in whom no endogenous GAA protein was detected by Western blot analysis and/or predicted antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained antibody titers, including CRIM-negative patients, may experience reduced clinical alglucosidase alfa treatment efficacy, such as loss of motor function, ventilator dependence, or death.

**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.
  - The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)].

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<tr>
<td>212526, 09/01/2020</td>
<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>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. (…).</td>
</tr>
</tbody>
</table>
| 212526, 09/01/2020                     | Alpelisib (3) | Oncology | PIK3CA | Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
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.

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.

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.

The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)]. (…).

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. (…).

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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>209321, 05/06/2019</td>
<td>Aminofampridine</td>
<td>Neurology</td>
<td>NAT2</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
<td>2.5 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers The recommended starting dosage of RUZURGI in pediatric patients weighing 45 kg or more who are known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily taken orally in divided doses. The recommended starting dosage in pediatric patients weighing less than 45 kg who are known NAT2 poor metabolizers is 7.5 mg daily taken orally in divided doses [see Dosage and Administration (2.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.5)].</td>
</tr>
<tr>
<td>208078, 11/28/2018</td>
<td>Aminofampridine Phosphate</td>
<td>Neurology</td>
<td>NAT2</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
<td>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 (8.8) and Clinical Pharmacology (12.3, 12.5)].</td>
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| 08/07/14   | 05971    | 07/17/2014   | Amoxapine | Psychiatry        | CYP2D6     | Precautions       | PRECAUTIONS: Drugs Metabolized by P450 2D6. The biodistribution of the drug metabolizing isozyme cytochrome P450 2D6 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 across 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. (…)
| 07/26/14   | 07/17/2014 | Amoxapine | Psychiatry | CYP2D6 | Precautions       | PRECAUTIONS: Drug Interactions. Drugs Metabolized by P450 2D6. The biodistribution of the drug metabolizing isozyme cytochrome P450 2D6 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 across 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. 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. (…)
| 20/4325    | 09/15/2017 | Amphetamine | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY | 12.3 Pharmacokinetics | Elimination | Metabolism and Excretion | 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 noramphetamine, respectively. Noramphetamine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, 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.
| 10/3950    | 12/18/2020 | Anakinra    | Rheumatology | NLRP3 | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE | 1.2 Cryopyrin-Associated Periodic Syndromes (CAPS) | 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 6 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. (…)

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<tr>
<td>12/13/2018</td>
<td>Anastrozole</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
</tbody>
</table>

1.1 Adjuvant Treatment
ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.

1.2 First-Line Treatment
ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer.

1.3 Second-Line Treatment
ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

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<tbody>
<tr>
<td>021912, 05/29/2019</td>
<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>A post-marketing trial assessed the combined effects of ARIMIDEX and the bisphosphonate risedronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture. (…)</td>
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<tr>
<td>021912, 05/29/2019</td>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>14.1 Adjuvant Treatment of Breast Cancer in Postmenopausal Women At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. (….)</td>
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<tr>
<td>021436, 02/23/2017</td>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration</td>
<td>7.1 Tamoxifen (2) Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial (see Clinical Studies (14.1)). Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole. (…)</td>
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<tr>
<td>Arispazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and</td>
<td>Dosage adjustment is recommended in known CYP2D6 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 (2.7) and CLINICAL PHARMACOLOGY (12.3)].</td>
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<tr>
<td>Lauroxil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Administration,</td>
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<td>Oncology</td>
<td>PML-RARA</td>
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<td>Studies</td>
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12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(...)(...) 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 Abilify (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults. (See Figure 4 and 5)

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), Clinical Pharmacology (12.3)].

Drug Interaction Studies

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 Cmax 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 Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 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)

1 INDICATIONS AND USAGE

1.1 Newly-Diagnosed Low-Risk APL

TRISENOX is indicated in combination with tretinoin 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.

14 CLINICAL STUDIES

14.1 Newly-Diagnosed Low-Risk APL

(...)(...) The trial enrolled 162 patients with a morphologic diagnosis of APL. The median age of patients was 45 years in the TRISENOX/tretinoin and 47 years in the chemotherapy/tretinoin arm, and 52% and 46% were male in the TRISENOX/tretinoin and chemotherapy/tretinoin arms, respectively. Baseline characteristics were balanced between treatment arms, including median WBC count, platelet count, PML-RAR isoform, and FLT3-ITD status. (…)

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<td>Atezolizumab (1)</td>
<td>Oncology</td>
<td>CD274</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions</td>
<td>1 INDICATIONS AND USAGE</td>
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<td></td>
<td>(PD-L1)</td>
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<td>1.4 Urothelial Carcinoma</td>
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<td>TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:</td>
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<td>• 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</td>
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<td>• are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or</td>
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<td>• have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.</td>
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<td>1.2 Non-Small Cell Lung Cancer</td>
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<td>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] ≥ 50% 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.</td>
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<td>1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer</td>
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<td>TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test (see Dosage and Administration (2.1)).</td>
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<td>This indication is approved under accelerated approval based on progression free survival (see Clinical Studies (14.3)). 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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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td></td>
<td>2.1 Patient Selection for Treatment of Urothelial Carcinoma and Triple-Negative Breast Cancer</td>
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<td>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)).</td>
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<td>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 of or on tumor infiltrating immune cells (see Clinical Studies (14.2)).</td>
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<td>Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells (see Clinical Studies (14.3)). Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma or triple-negative breast cancer are available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>3.5 Increased Mortality in Patients with Metastatic TNBC when TECENTRIQ is Used with Paclitaxel</td>
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<td>In a randomized trial in patients with metastatic TNBC an increase in the risk of death was observed in patients treated with TECENTRIQ plus paclitaxel compared with placebo and paclitaxel in the PD-L1-positive population. The efficacy of TECENTRIQ in combination with paclitaxel in patients with unresectable locally advanced or metastatic TNBC has not been demonstrated (see Indications and Usage (1.3) and Clinical Studies (14.4)). Do not substitute paclitaxel protein-bound with paclitaxel in combination with TECENTRIQ in clinical practice for metastatic TNBC outside of controlled trials.</td>
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<td>4 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>Non-small Cell Lung Cancer (NSCLC)</td>
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<td>IMpower110</td>
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<td>The safety of TECENTRIQ was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 649 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 33 months).</td>
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<td>(…) Previously: Treated Metastatic NSCLC</td>
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<td>(…) 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)).</td>
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<tr>
<td>761034, 12/22/2020</td>
<td>Articaine and Epinephrine (2)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.4 Methemoglobinemia</td>
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<td>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>
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</tbody>
</table>

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</table>

6.2 Immunogenicity
(…) Among 434 patients with TMB in IMpassion130, 13% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 178 patients in PD-L1 positive subgroup with TMB in IMpassion130, 15% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure [see Clinical Pharmacology (12.3)]. There are insufficient numbers of patients in the PD-L1 positive subgroup with ADA 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 (21–89 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 bilirubin > 1.0 to 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% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area). The remaining 73% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumor infiltrating IC covering < 5% of the tumor area).

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 87 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: 66% had impaired renal function, 28% had an ECOG PS of 2, 10% had a history 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 patients classified as having PD-L1 expression of < 5% when treated with TECENTRIQ monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The IDMC recommended closure of the monotherapy arm to further accrual of patients with low PD-L1 expression, however, no other changes were recommended for the study, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

Previously Treated 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 310 patients, 32% were classified as having PD-L1 expression of ≥ 5%. The remaining 68% of patients were classified as having PD-L1 expression of < 5%.

Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 23. The median follow-up time for this study was 32.9 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 831 12.3%, 34.7%). (See Table 23) (…) 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, and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5%. The remaining 68% of patients were classified as having PD-L1 expression of < 5%.

14.2 Non-Small Cell Lung Cancer
Metastatic Chemotherapy-Naïve NSCLC with High PD-L1 Expression
The efficacy of TECENTRIQ was evaluated in IMpower110 (NCT02400342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC] ≥ 1%) or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area [IC ≥ 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%), excluding those with EGFR or ALK genomic tumor aberrations. 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 2 weeks prior to randomization, or any of the following.

- Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure [see Clinical Pharmacology (12.3)]. There are insufficient numbers of patients in the PD-L1 positive subgroup with ADA 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.
# Table of Pharmacogenomic Biomarkers in Drug Labeling

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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 nonsquamous 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 4)

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 on ≥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 - 0.96) in patients who did not have high PD-L1 expression.

14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

(…) Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) (PD-L1 stained tumor-infiltrating immune cells [IC] ≥1% of tumor area) by the VENTANA PD-L1 (SP142) Assay. Of the 902 patients in the intent to treat population (ITT), 41% (369 patients) were classified as PD-L1 expression ≥ 1%. Patients were randomized to receive TECENTRIQ 840 mg or placebo intravenously on Days 1 and 15 of every 28-day cycle with paclitaxel 100 mg/m² intravenously on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks (±1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (±1 week) thereafter. Major efficacy outcomes were investigator-assessed progression-free survival (PFS) (per RECIST v1.1) and overall survival (OS) in the ITT population and PD-L1 expressing patient population. In IMpassion130, the median age was 55 years (range: 20-86). Overall, most patients were women (90%) and the majority of patients were white (68%), Asian (18%), Black or African American (7%), and American Indian or Alaskan Native (4%). The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Baseline ECOG performance status was 0 (56%) or 1 (41%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population.

Tumor specimens ( archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses. The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 28 and Figure 5.

14.4 Lack of Efficacy in Combination with Paclitaxel in Locally Advanced or Metastatic TNBC

The efficacy of TECENTRIQ in combination with paclitaxel in patients with unresectable locally advanced or metastatic triple-negative breast cancer has not been demonstrated. IMpassion131 (NCT03129502), a multicenter, international, double-blinded, placebo-controlled, randomized (1:1:1) trial that included 651 patients with unresectable locally advanced or metastatic triple-negative breast cancer that had not received prior chemotherapy for metastatic disease. Of these, 45% (PD-L1) expression ≥ 1% of tumor area were classified as PD-L1 expression ≥ 1%. Patients were randomized to receive TECENTRIQ 840 mg or placebo intravenously on Days 1 and 15 of every 28-day cycle with paclitaxel 90 mg/m² intravenously on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression or unacceptable toxicity. Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC). Patients with PD-L1 expression ≥ 1% of tumor area were randomized to receive TECENTRIQ or placebo. Tumor assessments were performed every 8 weeks. In IMpassion131, the median age was 55 years (range: 20-86). Overall, most patients were women (90%) and the majority of patients were white (68%), Asian (18%), Black or African American (7%), and American Indian or Alaskan Native (4%). The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Baseline ECOG performance status was 0 (56%) or 1 (41%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population.

Tumor specimens ( archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses. The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 28 and Figure 5.
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</table>
| 761034, 12/28/2020                   | Atezolizumab (3) | Oncology | EGFR | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Non-Small Cell Lung Cancer
- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic nonsquamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- 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. |
| 761034, 12/28/2020                   | Atezolizumab (4) | Oncology | ALK | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Non-Small Cell Lung Cancer
- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic nonsquamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations.
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<tr>
<td><strong>14.2 Non-Small Cell Lung Cancer</strong></td>
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<td><strong>Metastatic Chemotherapy-Naive NSCLC</strong></td>
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<td><strong>with PD-L1 Expression</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 stained ≥ 1% of tumor cells [TC] ≥ 1%) or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area [IC ≥ 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%), excluding those with EGFR or ALK genomic tumor aberrations. 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. (…)
| 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 ≥35% or IC ≥5%; and TC ≥21% or IC ≥11%.
| 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 (62%) and Asian (17%). Baseline ECOG performance status was 0 (36%) or 1 (64%); 88% were current or previous smokers; and 70% of patients had non-squamous disease while 24% of patients had squamous disease. (See Table 24 and Figure 1) (…)
| Metastatic Chemotherapy-Naive Non-Squamous NSCLC
| IMpower150
| (…) The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-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 subpopulation 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 ITT 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 12%, TC2/1 and IC2/3 in 13%, and TC0/1 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. (…) IMpower130
| (…) 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 and documented to have no EGFR or ALK genomic tumor aberrations (ITT-WT). (…)

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<tr>
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<td>Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>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.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.12 Laboratory Tests</td>
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<td>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)].</td>
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<td>5.13 Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients who are known to be CYP2D6 PMs</td>
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<td>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)].</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>Child and Adolescent Clinical Trials</td>
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<td>(…) 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); tremor (5% of PMs, 1% of EMs); exanthem (4% of PMs, 2% of EMs); middle insomnia (3% of PMs, 1% of EMs); conjunctivitis (3% of PMs, 1% of EMs); syncope (3% of PMs, 1% of EMs); early morning awakening (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs); sedation (4% of PMs, 2% of EMs). (…)</td>
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<td>Adult Clinical Trials</td>
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<td>(…) The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metabolizer (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); feeling jittery (5% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (6% of PMs, 2% of EMs); hyperhidrosis (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of EMs). (…)</td>
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<td>7 DRUG INTERACTIONS</td>
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<td>7.2 Effect of CYP2D6 Inhibitors on Atomoxetine</td>
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<td>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.</td>
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<td>In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.6 Hepatic Insufficiency</td>
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<td>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)].</td>
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<td>8.7 Renal Insufficiency</td>
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<td>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.</td>
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<td>8.9 Ethnic Origin</td>
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<td>Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics</td>
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<td>Cardiac Electrophysiology</td>
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<td>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 &gt;60 msec from baseline, absolute QTc &gt;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.</td>
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<td>12.3 Pharmacokinetics</td>
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<td>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 6 hours. A fraction of the population is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.</td>
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# Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 12/2020

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<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 021881, 12/07/2018                      | Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate | Gastroenterology | G6PD | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.8 Glucose-6-phosphate dehydrogenase (G-6-PD) Deficiency  
Since MoviPrep contains sodium ascorbate and ascorbic acid, MoviPrep 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. |
| 212608, 01/09/2020                      | Avapritinib | Oncology | PDGFRA | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)  
AVYKAT 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)].  
2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection for GIST Harboring PDGFRA Exon 18 Mutations  
Select patients for treatment with AVYKAT based on the presence of a PDGFRA exon 18 mutation [see Clinical Studies (14.1)]. An FDA-approved test for the detection of exon 18 mutations is not currently available.  
14 CLINICAL STUDIES  
14.1 Gastrointestinal Stromal Tumors  
Patients with GIST harboring a PDGFRA exon 18 mutation were identified by local or central assessment using a PCR- or NGS-based assay. The assessment of efficacy was based on a total of 43 patients, including 38 patients with PDGFRA D842V mutations. The median duration of follow up for patients with PDGFRA exon 18 mutations was 10.6 months (range: 0.3 to 24.9 months). The study population characteristics were median age of 64 years (range: 29 to 90 years), 67% were male, 67% were White, 93% had an ECOG PS of 0-1, 98% had metastatic disease, 53% had largest target lesion >5 cm, and 86% had prior surgical resection. The median number of prior kinase inhibitors was 1 (range: 0 to 5). 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) |
| 210238, 06/30/2019                      | Avatrombopag (1) | Hematology | F2 (Prothrombin) | 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=1/430) with chronic liver disease and (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)). (...) |
| 06/30/2019                              |                  |                  |                 |                  |               |

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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (2)</td>
<td>Hematology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Thrombotic/Thromboembolic Complications</td>
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<td>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 thrombocytopenia, 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.</td>
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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (3)</td>
<td>Hematology</td>
<td>PROC</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Thrombotic/Thromboembolic Complications</td>
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<td>210238, 06/30/2019</td>
<td>Avatrombopag (4)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
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<td>5.1 Thrombotic/Thromboembolic Complications</td>
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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (5)</td>
<td>Hematology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Thrombotic/Thromboembolic Complications</td>
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<td>210238, 06/30/2019</td>
<td>Avatrombopag (6)</td>
<td>Hematology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>The 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).</td>
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<td>761049, 06/30/2020</td>
<td>Avelumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Metastatic Merkel Cell Carcinoma</td>
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<td>(…) A total of 86 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 (≥ 1% of tumor 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 (MCPV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCPV. Efficacy results are presented in Table 8. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCPV.</td>
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<td>14.2 Locally Advanced or Metastatic Urothelial Carcinoma</td>
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<td>First-Line Maintenance Treatment of Urothelial Carcinoma</td>
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<td>(…) Fifty-six percent (56%) of patients received prior gemcitabine plus cisplatin. 38% of patients received prior gemcitabine plus carboplatin, and 6% of patients received gemcitabine plus cisplatin and gemcitabine plus carboplatin. Best response to first-line chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis prior to chemotherapy were visceral (55%) or nonvisceral (45%). Fifty-one (51%) of patients had PD-L1-positive tumors, 39% of patients had PD-L1-negative tumors, and 10% of patients had unknown PD-L1 tumor status. Six percent (6%) of patients received another PD-L1/PD-L1 checkpoint inhibitor after discontinuation of treatment in the AVENIO plus BSC arm and 44% of patients in the BSC arm.</td>
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<tbody>
<tr>
<td>016324, 12/20/2018</td>
<td>Azathioprine (1)</td>
<td>Rheumatology</td>
<td>TPMT</td>
<td>DOSAGE AND ADMINISTRATION</td>
<td>ullo Genetic Biomarkers in Drug Labeling</td>
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<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/PR 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, multicenter, open-label, study of BAVENCIO in combination with axitinib in 896 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 BICR 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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</table>
| 016324, 12/20/2018                     | Azathioprine  | Rheumatology      | NUDT15     | Dosage and Administration, Warnings, Precautions, Adverse Reactions, Clinical Pharmacology | patients 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 (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 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. (…)

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text²</th>
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</thead>
</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 Belinostat to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele [see Clinical Pharmacology (12.5)]. |
| 210498, 01/23/2019                      | Binimetinib (1)| Oncology          | BRAF       | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
MEKTOVI® 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)]. |
| 210498, 01/23/2019                      | Binimetinib (2)| Oncology          | UGT1A1     | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 20% of the black population, 10% of the white population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele. Additional reduced function alleles may be more prevalent in specific populations. Because belinostat is primarily (80-90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (e.g., patients with UGT1A1*28 allele). Reduce the starting dose of Belinostat to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities. |

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<tr>
<td>125557, 03/20/2020</td>
<td>Blinatumomab</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>Effect of UGT1A1 Inducers or Inhibitors on Blinatumomab: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on blinatumomab exposure. Simulations predict similar Cmax of blinatumomab 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).</td>
</tr>
<tr>
<td>202258, 01/30/2017</td>
<td>Boceprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
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<td></td>
<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 PegIntron/REBETOL. IL28B rs12979860 was genotyped in 663 of 1048 (62%) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPOND-2 (previous partial responders and relapers) [see Clinical Studies (14) for trial descriptions]. Among subjects who received at least one dose of placebo or VICTRELIS (Modified-Impent-to-Treat population), SVR rates tended to be lower in subjects with the C/T and T/T genotypes compared to those with the C/C genotype, particularly among previously untreated subjects receiving 48 weeks of PegIntron and REBETOL (see Table 9). Among previous treatment failures, subjects of all genotypes appeared to have higher SVR rates with regimens containing VICTRELIS. 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 substudy population relative to the overall trial population. (See Table 9)</td>
</tr>
<tr>
<td>203341, 10/09/2019</td>
<td>Bosutinib</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>2 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td></td>
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<td>BOSULIF is indicated for the treatment of adult patients with:</td>
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<td>• Newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates [see Clinical Studies (14, 15)]. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial.</td>
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<td>• Chronic phase, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
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<td></td>
<td>2.1 Recommended Dosing</td>
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<td>The recommended dose is taken orally once daily with food. The tablet is to be swallowed whole and should not be broken or cut. Continue treatment with BOSULIF until disease progression or intolerance to therapy.</td>
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<td>If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual prescribed dose on the following day.</td>
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<td>Newly-Diagnosed CP Ph+ CML</td>
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<td>The recommended dose of BOSULIF is 400 mg orally once daily with food.</td>
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<td>CP, AP, or BP Ph+ CML with Resistance or Intolerance to Prior Therapy</td>
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<td>The recommended dose and schedule of BOSULIF is 500 mg orally once daily with food.</td>
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<td>2.2 Dose Escalation</td>
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<td>In clinical studies of adult Ph+ CML patients, 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.</td>
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<td>2.5 Dose Adjustments for Renal Impairment or Hepatic Impairment</td>
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<td>The recommended starting doses for patients with renal and hepatic impairment are described in Table 2 below. (See Table 2)</td>
</tr>
</tbody>
</table>

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<td>125388, 10/15/2019</td>
<td>Brentuximab Vedotin (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Clinical Studies</td>
<td></td>
</tr>
<tr>
<td>125388, 10/15/2019</td>
<td>Brentuximab Vedotin (2)</td>
<td>Oncology</td>
<td>TNFRSF8 (CD30)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td></td>
</tr>
</tbody>
</table>

**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 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. (…) |

| 5.4 Fluid Retention |
| Fluid retention occurs with BOSULIF and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Monitor and manage patients using standards of care, including diuretics, and fluid replacement. In the randomized clinical trial of 268 patients with newly-diagnosed CML in the bosutinib treatment group, 1 patient (0.4%) experienced severe fluid retention of Grade 3 pericardial effusion. Among 546 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 26 patients (5%). Some patients experienced more than one fluid retention event. Specifically, 21 patients experienced Grade 3 or 4 pleural effusions, 7 patients experienced Grade 3 or 4 pericardial effusions, and 6 patients experienced Grade 3 edema. (…) |

**6 ADVERSE REACTIONS**

| 6.1 Clinical Trials Experience |
| Adverse Reactions in Patients With Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML The single-arm clinical trial enrolled patients with Ph+ CP, AP, or BP CML and with resistance or intolerance to prior therapy [see Clinical Studies (14)]. The safety population (received at least 1 dose of BOSULIF) included 546 CML patients: (…) |

| 8 USE IN SPECIFIC POPULATIONS |
| 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. |

**8.5 Geriatric Use**

| 14 CLINICAL STUDIES |
| The efficacy of BOSULIF in patients with newly-diagnosed chronic phase Ph+ CML was evaluated in the Bosutinib trial in First-line chrOmic 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” [NCT02130557]. 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 alone 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 (intent-to-treat [ITT] 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). Randomization was stratified by Sokal score and geographical region. All patients are being treated and/or followed for up to 5 years. Efficacy was evaluated in the MITT population. The major efficacy outcome measure was MMR at 12 months defined as ≤0.1% BCR-ABL ratio on international scale (corresponding to ≥3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts as assessed by the central laboratory. Additional efficacy outcomes included CD38+ by 12 months, defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable. (…) |

| 14.2 Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML |
| Study 200 (NCT00281946), 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 who were previously treated with 1 prior TKI (imatinib) or more than 1 TKI (imatinib followed by dasatinib and/or nilotinib). (See Table 5) (…) |

| 14.3 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 chrOmic 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” [NCT02130557]. 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 alone 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 (intent-to-treat [ITT] 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). Randomization was stratified by Sokal score and geographical region. All patients are being treated and/or followed for up to 5 years. Efficacy was evaluated in the MITT population. The major efficacy outcome measure was MMR at 12 months defined as ≤0.1% BCR-ABL ratio on international scale (corresponding to ≥3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts as assessed by the central laboratory. Additional efficacy outcomes included CD38+ by 12 months, defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable. (…) |

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<td>205422, 02/09/2018</td>
<td>Brexpiprazole</td>
<td>Psychiatry</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>2.5 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inducers or Inhibitors</td>
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<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 REXULTI dosage to its original level. If the coadministered CYP3A4 inhibitor is discontinued, reduce the REXULTI dosage to its original level over 1 to 2 weeks [see Drug Interactions (7.1), Clinical Pharmacology (12.3)]. (See Table 1)</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.6 CYP2D6 Poor Metabolizers</td>
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<td>Dosage adjustment is 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 REXULTI dosage to its original level over 1 to 2 weeks [see Drug Interactions (7.1), Clinical Pharmacology (12.3)]. (See Table 1)</td>
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<td>208772, 05/22/2020</td>
<td>Brigatinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>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 CYP2D6 and CYP3A4 inhibitors. A 4.9-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors [see Drug Interactions (7.1)].</td>
</tr>
<tr>
<td>205836, 05/12/2018</td>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>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>
</tbody>
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</table>
| 009386, 12/24/2003                     | Busulfan | Oncology | BCR-ABL1 (Philadelphia chromosome) | Clinical Studies | 14 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. (...)

| 203758, 01/31/2020                     | Cabozantinib | Oncology | RET | Clinical Studies | 14 CLINICAL STUDIES

(...)

Of 330 patients randomized, 67% were male, the median age was 55 years, 23% were 65 years or older, 89% were white, 54% had a baseline ECOG performance status of 0, and 92% had undergone a thyroidectomy. The RET mutation status determined by a research use assay was positive in 51%, negative in 14%, and was unknown in 34%. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI. (...)

| 02/08/16, 02/22/2019                  | Capcetabine | Oncology | DPYD | Warnings and Precautions, Patient Counseling Information | 5 WARNINGS AND PRECAUTIONS

5.4 Dihydropyrimidine Dehydrogenase Deficiency

Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene that result in complete or near complete absence of DPYD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPYD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA. Withhold or permanently discontinue XELODA 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 DPYD activity. There is insufficient data to recommend a specific dose in patients with partial DPYD activity as measured by any specific test.

| 213591, 05/06/2020                    | Capmatinib | Oncology | MET | Indications and Usage, Dosage and Administration, Clinical Studies | 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 a 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).

| 016608, 03/20/2018                    | Carbamazepine (1) | Neurology | HLA-B | Boxed Warning, Warnings, Precautions | BOXED WARNING

Serious dermatologic reactions and HLA-B*1502 allele

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. 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. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to therapy.

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<tbody>
<tr>
<td>03/20/2018</td>
<td>016608</td>
<td>Neurology</td>
<td>HLA-A</td>
<td><strong>WARNINGS</strong> Serious Dermatologic Reactions</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Warnings</td>
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<td></td>
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<td></td>
<td></td>
<td>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. <strong>SJS/TEN and HLA-B*1502 Allele</strong> Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B<em>1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity. Across Asian populations, notable variation exists in the prevalence of HLA-B</em>1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B<em>1502, averaging 2% to 4%, but higher in some groups. HLA-B</em>1502 is present in less than 1% of the population in Japan and Korea. HLA-B<em>1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). Prior to initiating Tegretol therapy, testing for HLA-B</em>1502 should be performed in patients with ancestry in populations in which HLA-B<em>1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B</em>1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Tegretol should not be used in patients positive for HLA-B<em>1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see BOXED WARNING and PRECAUTIONS, Laboratory Tests). Over 90% of Tegretol treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Tegretol. The HLA-B</em>1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from Tegretol such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Limited evidence suggests that HLA-B<em>1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B</em>1502 positive patients, when alternative therapies are otherwise equally acceptable. <strong>PRECAUTIONS</strong> Laboratory Tests For genetically at-risk patients (see WARNINGS), high-resolution ‘HLA-B<em>1502 typing’ is recommended. The test is positive if either one or two HLA-B</em>1502 alleles are detected and negative if no HLA B*1502 alleles are detected.</td>
</tr>
<tr>
<td>12/23/2019</td>
<td>022562</td>
<td>Inborn Errors of Metabolism</td>
<td>NAGS</td>
<td><strong>INDICATIONS AND USAGE</strong> <strong>1.1 Acute hyperammonemia in patients with NAGS deficiency</strong> 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. <strong>1.2 Chronic Hyperammonemia in Patients with NAGS Deficiency</strong> 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. <strong>INDICATIONS and Usage, Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical</strong></td>
</tr>
</tbody>
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<tbody>
<tr>
<td>204370, 05/24/2019</td>
<td>Cariprazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>12.3 Pharmacokinetics</td>
<td>CYP2D6 Poor Metabolizers</td>
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<td></td>
<td>CYP2D6 inhibitors do not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.</td>
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<td></td>
<td>Drug Interaction Studies</td>
</tr>
<tr>
<td>011792, 04/04/2019</td>
<td>Carisoprodol</td>
<td>Rheumatology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>8.3 Nonspecific Patients with reduced CYP2C19 Activity</td>
<td>Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients.</td>
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<tr>
<td></td>
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<td>Drug Interaction Studies</td>
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<tbody>
<tr>
<td>020297, 09/14/2017</td>
<td>Carvedilol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>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 carisoprodol, 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%.</td>
</tr>
<tr>
<td>020998, 05/03/2019</td>
<td>Celecoxib</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.7 Special Populations 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>
<tr>
<td>050585, 07/12/2018</td>
<td>Ceftriaxone (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings</td>
<td><strong>WARNINGS Methemoglobinemia</strong> 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>050585, 07/12/2018</td>
<td>Ceftriaxone (2)</td>
<td>Infectious Diseases</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td><strong>WARNINGS Methemoglobinemia</strong> 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>209750, 03/05/2019</td>
<td>Ceritinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration,</td>
<td><strong>1 INDICATIONS AND USAGE</strong> 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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<tr>
<td></td>
<td>Cerliponase Alfa</td>
<td>Inborn Errors of Metabolism</td>
<td>TPP1</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Studies</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>761052, 12/06/2019</td>
<td></td>
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<td></td>
<td></td>
<td>2.1 Patient Selection</td>
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<td>Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14.1)].</td>
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<td>Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC 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>Data in the Warnings and Precautions section reflect the safety of ZYKADIA 750 mg daily under fasted conditions in 925 patients with ALK-positive NSCLC across a pool of seven clinical studies at systemic exposures similar to the recommended dose of 450 mg with food. In a dose optimization study (ASCEND-8), there were no clinically meaningful differences observed in the incidence of toxicities described in Warnings and Precautions between patients receiving 750 mg daily under fasted conditions and 450 mg with food, except for a reduction in gastrointestinal adverse reactions as described [see Warnings and Precautions (5.1)].</td>
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<td></td>
<td>6 ADVERSE REACTIONS</td>
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<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 practice.</td>
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<td>The data in the Warnings and Precautions section reflect exposure to ZYKADIA 750 mg once daily in 925 patients with ALK-positive NSCLC across seven clinical studies, including ASCEND-4 and ASCEND-1, described below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies.</td>
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<td>In ASCEND-8, a dose optimization study, ZYKADIA 450 mg daily with food (N = 89) was compared to 750 mg daily under fasted conditions (N = 90) in both previously treated and untreated patients with ALK-positive NSCLC.</td>
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<td>Previously Untreated ALK-Positive Metastatic NSCLC</td>
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<td>The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study of 376 previously untreated ALK-positive NSCLC patients. Patients received ZYKADIA 750 mg daily (N=189) or chemotherapy plus maintenance chemotherapy (N=187).</td>
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<td>Previously Treated ALK-Positive Metastatic NSCLC</td>
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<td>The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in ASCEND-1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily). (See Tables 5 and 6)</td>
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<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.1 Previously Untreated ALK-Positive Metastatic NSCLC</td>
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<td>The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ASCEND-4, NCT01828099). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay.</td>
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<td>14.2 Previously Treated ALK-Positive Metastatic NSCLC</td>
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<td>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.</td>
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<td>The study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (64%), 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.</td>
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<td>1 INDICATIONS AND USAGE</td>
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<td>Brineura is indicated 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 peptide 1 (TPP1) deficiency.</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>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, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)].</td>
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<td>14 CLINICAL STUDIES</td>
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<td>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.</td>
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| 04/23/2019 | 125084              | 125084, 04/23/2019                      | Cetuximab (1)   | Oncology        | EGFR       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 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 when 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) (...)

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 FDA-approved tests for this use (see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Studies (14.2)): • in combination with FOLFIRI (irinotecan, 5-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. [See Warnings and Precautions (5.7), Clinical Pharmacology (12.1), Clinical Studies (14.2).]

Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.2 Colorectal Cancer

Determine EGFR-expression status using FDA-approved tests prior to initiating treatment. Also confirm the absence of a Ras mutation prior to initiation of treatment with Erbitux. Information on FDA-approved tests for the detection of K-Ras mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm

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 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 Monotherapy

(...) 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, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)]. ERBITUX was administered intravenously at the recommended dosage (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range 1 to 51) [see Clinical Studies (14.2)]. (See Table 5) (...)

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 CP02-9523 and BOND. (...)

14 CLINICAL STUDIES

14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)

In Combination with FOLFIRI

CRYSTAL (NCT00154102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)]. ERBITUX was administered intravenously at the recommended dosage (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range 1 to 51) [see Clinical Studies (14.2)]. (See Table 4) (...)

As Monotherapy

Study CA225-025 (NCT00079066) was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent mCRC. (See Table 9) (...)

In Combination with irinotecan

BOND was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. (...)

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 FDA-approved tests for this use [see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Studies (14.2)]: • in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment.

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# Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 12/2020

<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>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Precautions, Adverse Reactions, Clinical Studies</td>
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<td>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. [See Warnings and Precautions (5.7), Clinical Pharmacology (12.1), Clinical Studies (14.2).] Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)].</td>
</tr>
</tbody>
</table>

## 2 DOSAGE AND ADMINISTRATION

### 2.2 Colorectal Cancer
Determine EGFR-expression status using FDA-approved tests prior to initiating treatment. Also confirm the absence of a Ras mutation prior to initiation of treatment with Erbitux. Information on FDA-approved tests for the detection of K-Ras mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm

## 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 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)

(…) The safety of a cetuximab product in combination with FOLFIRI or 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 Monotherapy

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, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)]. (See Table 5) (…) In Combination with FOLFIRI

(…) The safety of the cetuximab product in combination with FOLFIRI or 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) (…) In Combination with FOLFIRI

### 14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)

(…) K-Ras mutation status was available for 89% of the patients: 63% had K-Ras wild-type tumors and 37% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. Baseline characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population. (…) Results of the planned PFS and ORR analysis in all randomized patients and post-hoc PFS and ORR analysis in subgroups of patients defined by K-Ras mutation status, and post-hoc analysis of updated OS based on additional followup (1000 events) in all randomized patients and in subgroups of patients defined by K-Ras mutation status are presented in Table 8 and Figure 2. The treatment effect in the all-randomized population for PFS was driven by treatment effects limited to patients who have K-Ras wild-type tumors. There is no evidence of effectiveness in the subgroup of patients with K-Ras mutant tumors. (See Table 8 and Figure 2) (…) K-Ras status was available for 79% of the patients: 54% had K-Ras wild-type tumors and 46% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. (See Table 9 and Figure 3) (…) In Combination with Irinotecan

BOND was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. (…) In Combination with Irinotecan

### 14 CLINICAL STUDIES

(Bond was a multicenter clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status.)

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</thead>
<tbody>
<tr>
<td>011641, 02/01/2011</td>
<td>Chlorpropamide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td></td>
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<td></td>
<td></td>
<td>PRECAUTIONS</td>
</tr>
<tr>
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<td></td>
<td>Hemolytic Anemia</td>
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<tr>
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<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>
<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
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<td>WARNINGS</td>
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<td>Methemoglobinemia</td>
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<td>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>009435, 11/02/2018</td>
<td>Chloroprocaine</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
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<td>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>
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<tr>
<td>205750, 10/22/2020</td>
<td>Cholic Acid</td>
<td>Inborn Errors of Metabolism</td>
<td>AMACR, AKR1D1, CYP7A1, CYP27A1, DHCR7, HSD3B2 (Bile Acid Synthesis Disorders)</td>
<td>1 INDICATIONS AND USAGE</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>1.1 Bile Acid Synthesis Disorders Due to Single Enzyme Defects</td>
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<td>CHOLBAM is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).</td>
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<td>1.3 Limitations of Use</td>
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<td>The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PIDs including Zellweger spectrum disorders have not been established.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Dosage Regimen for Bile Acid Synthesis Disorders Due to SEDs and PIDs Including Zellweger Spectrum Disorders</td>
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<td>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. (…)</td>
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<td>2.2 Treatment Monitoring</td>
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<td>(…) 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 PIDs 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.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Exacerbation of Liver Impairment</td>
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<td>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 due to SEDs and in approximately 50% (14/28) of patients with PIDs including Zellweger spectrum disorders. Five of the patients (3SED and 2 PDX) with liver impairment at baseline experienced worsening liver transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy following treatment. Five additional patients (2 SED and 3 PDX) 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.</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>Clinical safety experience with CHOLBAM consists of:</td>
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<td>• 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 PIDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.</td>
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<td>• Trial 2: an extension trial of 12 new patients (10 SED and 2 PDX) along with 31 (21 SED and 10 PDX) patients who rolled over from Trial 1. Safety data are available for 3 years and 11 months of treatment. (…)</td>
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<td>Deaths</td>
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<td>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 36-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 PIDs 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 PDX) 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.</td>
</tr>
</tbody>
</table>

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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>018057, 02/22/2019</td>
<td>Cisplatin</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>Ototoxicity</td>
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<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>
</tr>
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<td></td>
<td>Special Populations</td>
</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>WARNINGS</td>
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<td>QT-Prolongation and Torsade de Points</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>
</tr>
</tbody>
</table>

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<tr>
<td>020822, 01/11/2019</td>
<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>
</tbody>
</table>
| 202067, 06/15/2018                     | Clobazam | Neurology | CYP2C19 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION

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)]. |
| 019908, 05/10/2019                     | Clomipramine | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 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). (…) |
| 020839, 05/17/2019                     | Clopidogrel | Cardiology | CYP2C19 | Boxed Warning, Warnings and Precautions, Clinical Pharmacology | BOXED WARNING

WARNING

Diminished antiplatelet effect in patients with two loss-of-function alleles of the CYP2C19 gene

The effectiveness of Plavix results from its antiplatelet 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. |

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<tbody>
<tr>
<td>019758, 02/23/2017</td>
<td>Codeine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. Patients who are homozygous for nonfunctional alleles of the CYP2C19 gene are termed “CYP2C19 poor metabolizers”. Approximately 2% of White and 4% of Black patients are poor metabolizers; the prevalence of poor metabolism is higher in Asian patients (e.g., 14% of Chinese). Tests are available to identify patients who are CYP2C19 poor metabolizers. A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and platelet response using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. (See Table 3)</td>
</tr>
</tbody>
</table>
| 206192, 01/26/2018                     | 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
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 is available at: http://www.fda.gov/CompanionDiagnostics

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…) The safety of COVELLIC® 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)]. (…) |
| 022402, 09/18/2018                     | Codeine | Anesthesiology | CYP2D6 | Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information | BOXED WARNING
WARNING: ADDICTION, ABUSE, AND MISUSE; LIFETHREATENING 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
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 an 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 16 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. (…) |

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<tr>
<td>761128, 11/15/2019</td>
<td>Crizanlizumab-tmca</td>
<td>Hematology</td>
<td>HBB</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>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 adenectomy, 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 adenectomy 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 &quot;1<em>1xN or 1</em>2xN&quot;). 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 American), 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 Overdose (10)]. Therefore, individuals who are ultra-rapid metabolizers should not use Codeine Sulfate Tablets.</td>
</tr>
<tr>
<td>202570, 06/25/2019</td>
<td>Crizotinib (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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 dangerously 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 adenectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isocyneme 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 adenectomy. 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)].</td>
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| 06/25/2019 | 202570, 06/25/2019 | Crizotinib (2) | Oncology | ROS1 | 6.1 Clinical Trials Experience | (…) The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm), 2, 3, a single arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose-finding study (n=154). 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). (…) Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014) The data in Table 3 are derived from 343 patients with ALK-positive metastatic NSCLC who had not received previous systemic treatment for advanced disease who received treatment in a randomized, multicenter, open-label, active-controlled trial (Study 1). (…) Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007) The data in Table 5 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 2). (…) 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. Renal toxicity The estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m² (n=1681) to a median of 80.23 mL/min/1.73 m² at 2 weeks (n=1486) in patients with ALK-positive advanced NSCLC who received XALKORI in clinical trials. (…)

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. (…)

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics Cardiac electrophysiology In an ECG substudy conducted in 52 patients with ALK-positive NSCLC who received crizotinib 250 mg twice daily, the maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was 12.3 ms (2-sided 90% upper CI: 19.5 ms). An exposure-QT analysis suggested a crizotinib plasma concentration dependent increase in QTcF [see Warnings and Precautions (5.3)].

14.1 ALK-Positive Metastatic NSCLC Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014; NCT01154410) The efficacy and safety 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. (See Table 7) (…) Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007; NCT00932893) The efficacy and safety 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). (…) (…) 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. A total of 112 (64%) patients randomized to the chemotherapy arm subsequently received XALKORI after disease progression. (See Table 8) (…)

1 INDICATIONS AND USAGE 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.

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (…) 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). (…)

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| 202806, 04/09/2020                     | Dabrafenib (1) | Oncology | BRAF | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information | 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.  
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  
14.2 ROS1-Positive Metastatic NSCLC  
**ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001; NCT00585195)**  
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 IRF 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 (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (8%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) 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. (See Table 9)  

### 1 INDICATIONS AND USAGE  
1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma  
**TAFINLAR® is indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)].**  
1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma  
**TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)].**  
1.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma  
**TAFINLAR is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see Dosage and Administration (2.1), (2.3)].**  
1.4 BRAF V600E Mutation-Positive Metastatic NSCLC  
**TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.4)].**  
1.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer  
**TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)].**  
1.6 Limitations of Use  
**TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC [see Warnings and Precautions (5.2)].**  

### 2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent [see Warnings and Precautions (5.2) and Clinical Studies (14.1)].  
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Warnings and Precautions (5.2), Clinical Studies (14.2), (14.3)].  
- Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: [http://www.fda.gov/CompanionDiagnosticsNSCLC](http://www.fda.gov/CompanionDiagnosticsNSCLC).  
- Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: [http://www.fda.gov/CompanionDiagnosticsATC](http://www.fda.gov/CompanionDiagnosticsATC).  

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<td>COMBI-d Study and COMBI-M Study</td>
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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 (14.5)]. An FDA-approved test for the detection of BRAF V600E mutation in ATC 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 section reflect exposure to TAFINLAR administered as a single agent in 580 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 580 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 330 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 83 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). (…)

### 12 CLINICAL PHARMACOLOGY

#### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

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 IRCO 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-MR**

The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, two-cohort multicenter trial (the BREAK-MB study; NCT01266967). (…)

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

COMBI-d Study and COMBI-m Study

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The safety and efficacy of RAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01684648) and one open-label trial (the COMBI-v study; NCT01597908). The COMBI-d study compared RAFINLAR and trametinib to 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 RAFINLAR 150 mg twice daily and trametinib 2 mg once daily or placebo 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 RAFINLAR 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 RAFINLAR 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 RAFINLAR 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, 87% had a normal LDH, 70% had ECOG performance status of 0, 86% 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, 85% had a normal LDH value at baseline, and 97% had an ECOG performance status of 0 or 1. Intransit 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 Adjunctive 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 THold™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or placebo 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 treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIIA, IIIB, or IIIC). (…)

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 IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%), BRAF V600E mutation (91%), BRAF V600K mutation (9%), macroscopic lymph node(s) (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)

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

The safety and efficacy of RAFINLAR administered with trametinib 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. Trial BRF117019 excluded patients who could not swallow or retain medication. (…)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

Confirmation of BRAF V600E mutation
• RAFINLAR as a single agent: Evidence of BRAF V600E mutation in the tumor specimen using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)].

• RAFINLAR with trametinib: Evidence of BRAF V600E mutation in tumor specimens using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)].

5 WARNINGS AND PRECAUTIONS

5.9 Glucose-6-Phosphate Dehydrogenase Deficiency

RAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking RAFINLAR.

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| 202806, 04/09/2020                      | Dacomitinib (3) | Oncology | RAS | Counseling Information | 6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Metastatic or Unresectable BRAF V600E or V600K Mutation-Positive Melanoma  
TAFINLAR as a Single Agent  
Table 3 and Table 4 present adverse drug reactions 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 = 167) or dacarbazine 1,000 mg/m² intravenously every 3 weeks (n = 63). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥ Grade 2), corrected QT interval greater than or equal to 480 milliseconds on electrocardiogram, or a known history of glucose-6-phosphate dehydrogenase deficiency. (…)  
17 PATIENT COUNSELING INFORMATION  
Glucose-6-phosphate dehydrogenase (G6PD) deficiency  
TAFINLAR may cause hemolytic anemia in patients with G6PD deficiency. Advice patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis [see Warnings and Precautions (5.6)].  
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)  
5 WARNINGS AND PRECAUTIONS  
5.1 New Primary Malignancies  
Non-cutaneous Malignancies  
Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Across clinical trials of TAFINLAR monotherapy and TAFINLAR administered with trametinib, non-cutaneous malignancies occurred in 1% of patients. Monitor patients receiving TAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies [see Dosage and Administration (2.7)]. |
| 206843, 11/09/2017                     | Daclatasvir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 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, 5% were Asian, and 4% were black. Most subjects (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU per 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 baseline NS5A 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 per mL; 16% of the subjects had compensated cirrhosis, and 73% had IL28B rs12979860 non-CC genotype. (…)  
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, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6, 7% 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 NS5A amino acid polymorphisms, see Microbiology (12.4). (…) |
| 211298, 09/27/2018                     | Dacomitinib | Oncology | EGFR | Indications and Usage | 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: http://www.fda.gov/Drugs/CompanionDiagnostics.  
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 who received VIZIMPRO at the recommended dose of 45 mg once daily in 4 randomized, active-controlled trials [ARCHER 1050 (N=227), Study AT7471009 (N=38), Study AT7471011 (N=83), and Study AT7471028 (N=16)]. |

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<td>021794, 05/18/2018</td>
<td>Dapsone (1)</td>
<td>Dermatology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>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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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 orally once daily [ARCHER 1050 (N=227), Study A7471009 (N=58), Study A7471011 (N=83), Study A7471028 (N=16), and Study A7471017 (N=30)], 40% were 65 years of age and older. (…) 14 CLINICAL STUDIES

The efficacy of VIZIMPRO was demonstrated in a randomized, multicenter, multinational, open-label study (ARCHER 1050; [NCT01774721]). Patients were required to have unresectable, metastatic NSCLC with no prior therapy for metastatic disease or recurrent disease with a minimum of 12 months disease-free after completion of systemic therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; EGFR exon 19 deletion or exon 21 L858R substitution mutations. EGFR mutation status was prospectively determined by local laboratory or commercially available tests (e.g., therascreen® EGFR RQ PCR and cobas® EGFR Mutation Test). Patients were randomized (1:1) to receive VIZIMPRO 45 mg orally once daily or gefitinib 250 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by region (Japanese versus mainland Chinese versus other East Asian versus non-East Asian), and EGFR mutation status (exon 19 deletions versus exon 21 L858R substitution mutation). (…) Prognostic and tumor characteristics were ECOG performance status 0 (30%) or 1 (70%); 59% with exon 19 deletion and 41% with exon 21 L858R substitution; Stage IIIIB (8%) and Stage IV (92%); 64% were never smokers; and 11% received prior adjuvant or neoadjuvant therapy. (…) 5.2 Hematologic Effects

Oral dapsone 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 dapsone or antimalarial 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 dapsone in breastmilk, the effects on the breastfed infant, or the effects on milk production. Orally administered dapsone appears in human milk and could result in hemolytic anemia and hyperbilirubinemia especially in infants with G6PD deficiency. Systemic absorption of dapsone following topical application is minimal relative to oral dapsone administration; however, it is known that dapsone is present in human milk following administration of oral dapsone. 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 haptoglobin or lactate dehydrogenase during ACZONE® or 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 had such decreases during ACZONE® treatment compared to 7 of 56 subjects during vehicle treatment). 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

Advise the patient to read the FDA-approved patient labeling (Patient Information). Hematologic Effects

• Inform patients that methemoglobinemia can occur with topical dapsone 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 dapsone treatment. Advise patients to seek medical attention if they develop signs and symptoms suggestive of hemolytic anemia [see Warnings and Precautions (5.2)].

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| 021794, 05/18/2018                    | Dapsone (2) | Dermatology      | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions, Adverse Reactions, Patient Counseling Information | 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 initiation. 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. |
| 021513, 03/15/2012                    | Darifenacin | Urology          | CYP2D6     | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
Electrophysiology  
The effect of six-day treatment of 15 mg and 75 mg Enablex on QT/QTc interval was evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44 percent male, 56 percent female) aged 18 to 65. Subjects included 18 percent poor metabolizer (PMs) and 82 percent extensive metabolizer (EMs). The QT interval was measured over a 24-hour period both predosing and at steady-state. The 75 mg Enablex dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, Enablex did not result in QT/QTc interval prolongation at any time during the steady-state, while moxifloxacin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the clinical efficacy and safety studies, the change in mean HR following treatment with Enablex was no different from placebo. |
| 066841                                | Dapsone (3)  | Infectious Diseases | G6PD | Precautions, Adverse Reactions, Overdose | Labeling not electronically available on Drugs@FDA |
| 021513, 03/15/2012                    | Darifenacin | Urology          | CYP2D6     | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Absorption  
After oral administration of Enablex to healthy volunteers, peak plasma concentrations of darifenacin are reached approximately seven hours after multiple dosing and steady-state plasma concentrations are achieved by the sixth day of dosing. The mean (SD) steady-state time course of Enablex 7.5 mg and 15 mg extended-release tablets is depicted in Figure 1.  
A summary of mean (standard deviation, SD) steady-state pharmacokinetic parameters of Enablex 7.5 mg and 15 mg extended-release tablets in EMs and PMs of CYP2D6 is provided in Table 3.  
The mean oral bioavailability of Enablex in EMs at steady-state is estimated to be 15 percent and 19 percent for 7.5 mg and 15 mg tablets, respectively. (See Figure 1 and Table 3)  
Variability in Metabolism  
A subset of individuals (approximately 7 percent Caucasians and 2 percent African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs.  
Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM versus EM) for Cmax and AUC following darifenacin 15 mg once daily at steady-state were 1.9 and 1.7, respectively.  
Excretion  
Following administration of an oral dose of 14C-darifenacin solution to healthy volunteers, approximately 60 percent of the radioactivity was recovered in the urine and 40 percent in the feces. Only a small percentage of the excreted dose was unchanged darifenacin (3 percent). Estimated darifenacin clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life of darifenacin following chronic dosing is approximately 13 to 16 hours. |
| 021794, 05/18/2018                    | Dapsone (2) | Dermatology      | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions, Adverse Reactions, Patient Counseling Information | 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 initiation. 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. |

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<td>14 CLINICAL STUDIES</td>
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## 14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis

Subjects with Chronic HCV GT1a Infection without Cirrhosis

- Subjects with HCV GT1a infection without cirrhosis treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV [see Clinical Studies (14.1)] had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 19% had a body mass index of at least 30 kg per m²; 55% of patients were enrolled in US sites; 72% had IL28B (rs12979860) non-CC genotype; 85% had baseline HCV RNA levels of at least 800,000 IU per mL. (…)

Subjects with HCV GT1b infection without cirrhosis treated with VIEKIRA PAK with or without RBV for 12 weeks in PEARL-II and -III [see Clinical Studies (14.1)]. Subjects had a median age of 52 years (range: 22 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were 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) non-CC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per mL. (…)

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

Subjects with Chronic HCV GT1a Infection and Compensated Cirrhosis

- TURQUOISE-III was an open-label trial that enrolled 60 HCV GT1b-infected subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naïve or who did not achieve SVR with prior treatment with pegIFN/RBV. Subjects received VIEKIRA PAK without RBV for 12 weeks. Treated subjects had a median age of 61 years (range: 26 to 78); including 45% treatment-naïve and 55% pegIFN/RBV treatment-experienced; 25% were ≤65 years; 62% were male; 12% were Black; 5% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m²; 40% of patients were enrolled in US sites; 22% had platelet counts of less than 90 x 10⁹ per L; 17% had albumin less than 35 g/L; 92% had baseline HCV RNA levels of at least 800,000 IU per mL; 83% had IL28B (rs12979860) non-CC genotype; (…)

## 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 were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection. (…)

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For adults with Ph+ CML and ALL, and pediatric patients with Ph+ CML, if a severe nonhematologic adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event. For pediatric patients with Ph+ ALL, interrupt treatment for cases of grade > 3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade <1.

2.6 Duration of Treatment
In clinical studies, treatment with SPRYCEL in adults and in pediatric patients with chronic phase CML was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response (CCyR)) or major molecular response (MMR and MR4.5) has not been established. In clinical studies, treatment with SPRYCEL in pediatric patients with Ph+ ALL was administered for a maximum duration of 2 years. SPRYCEL is an antineoplastic product.

Follow applicable special handling and disposal procedures.

5 WARNINGS AND PRECAUTIONS

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, 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 2388 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 39%. Among the 1618 SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to disconnection were reported in 329 (20.3%) patients; among the 1094 SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, drug-related adverse events leading to disconnection were reported in 191 (17.5%) patients.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults
A total of 136 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 multagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL. [See Clinical Studies (14.4)]. The median duration of therapy was 24 months (range 2–27 months). (See Tables 14 and 15)

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

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|                                       |                                |                   |            |                   | 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 (5.10)]. Ph+ ALL
The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients 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 (5.10)]. 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
(…) BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317L, and V299L. Dasatinib does not appear to be active against the T315I mutation, based on in vitro data.
14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults
The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib:
1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL.
In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months); or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. (…)
(…) The primary efficacy endpoint in chronic phase CML was MCyR; defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).
Advanced Phase CML and Ph+ ALL Dose-Optimization Trial: One randomized open-label trial was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. (See Table 19) (…) (…) In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twice-daily were 4.0 months (min-max: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively.
14.4 Ph+ ALL in Pediatric Patients
The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a single cohort (cohort 1) of Study CA180372 (NCT01460160), a multicenter, multiple-cohort study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. The 78 patients in cohort 1 received SPRYCEL at a daily dose of 60 mg/m² for up to 24 months, in combination with chemotherapy. The backbone chemotherapy regimen was the AIEOP-BFM ALL 2000 multi-agent chemotherapy protocol. (…)

103767, 02/10/2020 Denileukin Diftitox Oncology IL2RA (CD25 antigen) Indications and Usage, Clinical Studies 1 INDICATIONS AND USAGE
Ontak is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the II-2 receptor.

14 CLINICAL STUDIES
14.1 Study 1: Placebo Controlled Study in CTCL (Stage Ia to III Patients)
The safety and efficacy of Ontak were evaluated in a randomized, double-blind, placebo-controlled, 3-arm trial in patients with Stage Ia to III CD25(+) CTCL.
Eligible patients were required to have expression of CD25 on ≥20% of biopsied malignant cells by immunohistochemistry [see Warnings and Precautions (5.4)]. (…)
14.2 Study 2: Dose Evaluation Study in CTCL (Stage Iib to Iva) Patients
A randomized, double-blind study was conducted to evaluate doses of 9 or 18 mcg/kg/day in 71 patients with recurrent or persistent. Stage Iib to Iva CTCL. Entry to this study required demonstration of CD25 expression on at least 20% of the cells in any relevant tumor tissue sample (skin biopsy) or circulating cells. Tumor biopsies were not evaluated for expression of other IL-2 receptor subunit components (CD122/CD132). (…)

014399, 11/09/2018 Desipramine Psychiatry CYP2D6 Precautions PRECAUTIONS
Drug Interactions 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). (…)

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| 020118, 03/01/2019                     | Desflurane          | Anesthesiology    | Nonspecific (Genetic Susceptibility to Malignant Hyperthermia) | Contraindications | The use of SUPRANE is contraindicated in the following conditions:  
* Known or suspected genetic susceptibility to malignant hyperthermia. (…)* |
| 021992, 02/06/2018                     | Desvenlafaxine      | Psychiatry        | CYP2D6     | Pharmacology                      | Pharmacology    |
| 208082, 06/06/2018                     | Deutetrabenazine    | Neurology         | CYP2D6     | Pharmacology                      | Pharmacology    |
|                                        |                     |                   |            | Dosage and Administration         | 2.4             |
|                                        |                     |                   |            | 2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers                 | 2.4             |
|                                        |                     |                   |            | In patients who are poor CYP2D6 metabolizers, the total daily | 2.4             |
|                                        |                     |                   |            | dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) | 2.4             |
|                                        |                     |                   |            | [see Use in Specific Populations (8.7)]. | 2.4             |
|                                        |                     |                   |            | (…) A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor [see Clinical Pharmacology (12.2, 12.3)]. | 2.4             |
|                                        |                     |                   |            | For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary [see Dosage and Administration (2.3, 2.4)]. | 2.4             |
|                                        |                     |                   |            | The use of AUSTEDO in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongations [see Drug Interactions (7.2)]. | 2.4             |
|                                        |                     |                   |            | (…) A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor, dose reduction may be necessary [see Dosage and Administration (2.3, 2.4)]. | 2.4             |
|                                        |                     |                   |            | 8.7 USE IN SPECIFIC POPULATIONS | 8.7             |
|                                        |                     |                   |            | 8.7 Poor CYP2D6 Metabolizers | 8.7             |
|                                        |                     |                   |            | Although the pharmacokinetics of deutetrabenazine 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). | 8.7             |
|                                        |                     |                   |            | In patients who are poor CYP2D6 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)]. | 8.7             |
|                                        |                     |                   |            | 12 CLINICAL PHARMACOLOGY | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | 12.3 Pharmacokinetics | 12.3 Pharmacokinetics |
|                                        |                     |                   |            | Poor CYP2D6 Metabolizers | Poor CYP2D6 Metabolizers |
|                                        |                     |                   |            | Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, 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). | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | Strong CYP2D6 inhibitors [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | 12.3 Pharmacokinetics | 12.3 Pharmacokinetics |
|                                        |                     |                   |            | Poor CYP2D6 Metabolizers | Poor CYP2D6 Metabolizers |
|                                        |                     |                   |            | Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | drug metabolizing enzyme CYP2D6, 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). | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | Strong CYP2D6 inhibitors [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. | 12 CLINICAL PHARMACOLOGY |
| 022287, 06/07/2018                     | Dexlansoprazole      | Gastroenterology  | CYP2C19    | Pharmacology                      | Pharmacology    |
|                                        |                     |                   |            | Dosage and Administration, | 7 DRUG INTERACTIONS |
|                                        |                     |                   |            | Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 7 DRUG INTERACTIONS |
|                                        |                     |                   |            | Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. | 7 DRUG INTERACTIONS |
|                                        |                     |                   |            | 12 CLINICAL PHARMACOLOGY | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | 12.3 Pharmacokinetics | 12.3 Pharmacokinetics |
|                                        |                     |                   |            | Metabolism | Metabolism |
|                                        |                     |                   |            | (…) CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates: extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite. | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | Cytochrome P 450 Interactions | Cytochrome P 450 Interactions |
|                                        |                     |                   |            | (…) Although in vitro studies indicated that DEXILANT has the potential to inhibit CYP2C19 in vivo, an in vivo drug-drug interaction study in mainly CYP2C19 extensive and intermediate metabolizers has shown that DEXILANT does not affect the pharmacokinetics of diazepam (CYP2C19 substrate). (…) | 12 CLINICAL PHARMACOLOGY |
|                                        |                     |                   |            | Clopidogrel | Clopidogrel |
|                                        |                     |                   |            | Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with DEXILANT 60 mg capsules (n=40), for nine days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 86-97%) when DEXILANT was coadministered compared to administration of clopidogrel alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (reduced by 5 mCM ADP) was related to the change in the exposure to clopidogrel active metabolite. The effect on exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important. | 12.5 Pharmacogenomics |
|                                        |                     |                   |            | Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole | 12.5 Pharmacogenomics |

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</table>
| 021879, 06/11/2019                    | Dextromethorphan and Quinidine | Neurology         | CYP2D6     | Warnings and Precautions, Clinical Pharmacology | 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)].  
5.8 CYP2D6 Poor Metabolizers  
The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3), (12.5)]. Approximately 7%-10% of Caucasians and 3%-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA. |

| 028488, 12/16/2016                   | Diazepam       | Neurology         | CYP2C19     | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
Cardiac Electrophysiology  
The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo- and positive controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for dextromethorphan 30 mg/quinidine 10 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype. |

| 125516, 03/01/2017                   | Dinutuximab    | Oncology          | MYCN       | Clinical Studies | 14 CLINICAL STUDIES  
(3) 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. |

| 022234, 10/11/2019                   | Docetaxel      | Oncology          | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES  
14.2 Adjuvant Treatment of Breast Cancer  
(3) 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). |

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<td>020660, 12/18/2018</td>
<td>Donepezil</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>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 isoenzymes 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 (53%) and as 6-oxo-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. Examination of the effect 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.</td>
</tr>
<tr>
<td>020286, 03/17/2010</td>
<td>Doxepin (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5. Special Population Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
<tr>
<td>020286, 03/17/2010</td>
<td>Doxepin (2)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5. Special Population Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
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<td>205525, 09/14/2018</td>
<td>Dronabinol</td>
<td>Gastroenterology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.6 Effect of CYP2C9 Polymorphism Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function [see Clinical Pharmacology (12.5)].</td>
</tr>
<tr>
<td>021676, 08/09/2017</td>
<td>Drospirenone and Ethinyl Estradiol</td>
<td>Gynecology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Effects of Combined Oral Contraceptives on Other Drugs (...) In the study with 24 postmenopausal women [including 12 women with homozygous (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>
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<tr>
<td>021427, 12/19/2017</td>
<td>Duloxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS 7.3 Dual Inhibition of CYP1A2 and CYP2D6 Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.</td>
</tr>
<tr>
<td>76109, 06/05/2020</td>
<td>Durvalumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Specific Populations Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance (CLcr) 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status had no clinically significant effect on the pharmacokinetics of durvalumab. (...)</td>
</tr>
<tr>
<td>211155, 09/26/2019</td>
<td>Duvelisib</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Efficacy in Relapsed or Refractory CLL/SLL Study (...) In this subset (95 randomized to COPIKTRA, 101 to flatumab), 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. (...)</td>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</thead>
</table>
| 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.

14 CLINICAL STUDIES
14.3 Generalized Myasthenia Gravis (gMG)
The efficacy of Soliris for the treatment of gMG was established in gMG Study 1 (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multi-center trial that enrolled patients who met the following criteria at screening: 1. Positive serologic test for anti-AChR antibodies, 2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV, 3. MG-Activities of Daily Living (MG-ADL) total score ≥26. Failing treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVig). (…)

| 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.

14 CLINICAL STUDIES
14.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)
The efficacy of Soliris for the treatment of NMOSD was established in NMOSD Study 1 (NCT01892345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening: 1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening, 2. Expanded Disability Status Scale (EDSS) score ≤7 (consistent with the presence of at least limited ambulation with aid), 3. On immunosuppressive therapy (IST), on a stable dose regimen, 4. The use of concurrent corticosteroids was limited to 20 mg per day or less, 5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IV Ig within 3 weeks prior to screening, (…)

| 020972, 10/10/2017                   | Efavirenz    | Infectious Diseases | CYP2B6  | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of SUSTIVA 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/*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 was 8.7 ms and 11.3 ms in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days (see Warnings and Precautions (5.2)).

| 210450, 07/23/2018                   | Elagolix     | Gynecology         | SLC01B1  | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
Disposition of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in groups of patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521C/C genotype). The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. Subjects with this genotype are expected to have a 78% mean increase in elagolix concentrations compared to subjects with normal transporter function (i.e., SLC01B1 521T/T genotype).

| 208261, 06/28/2018                   | Ebsavir and Grazoprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14 CLINICAL STUDIES
14.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE CONFECTION)
(…) C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naïve subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized in a 3:1 ratio to: ZEPATIER for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with ZEPATIER for 12 weeks (deferred treatment group). Among subjects with genotype 1 infection randomized to the immediate treatment group, the median age was 55 years (range: 20 to 78); 56% of the subjects were male; 61% were White; 20% were Black or African American; 8% were Hispanic or Latino; mean body mass index was 26 kg/m²; 72% had baseline HCV RNA levels greater than 800,000 IU per mL; 24% had cirrhosis; 87% had non-C/C IL28B alleles (CT or TT); and 55% had genotype 1a and 45% had genotype 1b chronic HCV infection. C-EDGE CONFECTION was an open-label, single-arm trial in treatment-naïve 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 53 years (range: 21 to 71); 80% of the subjects were male; 75% were White; 19% were Black or African American; 6% were Hispanic or Latino; mean body mass index was 25 kg per m²; 59% had baseline HCV RNA levels greater than 800,000 IU per mL; 16% had cirrhosis; 85% 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. (…) 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 co-infection, who had failed prior therapy with PegIFN + 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 co-infection, who had failed prior 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

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**Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies**

**1 INDICATIONS AND USAGE**

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.

**8 USE IN SPECIFIC POPULATIONS**

**8.4 Pediatric Use**

The safety and effectiveness of TRIKAFTA in the treatment of CF in pediatric patients 12 years and older who have at least one F508del mutation in the CFTR gene has been established. Use of TRIKAFTA for this indication was supported by evidence from two adequate and well-controlled studies in CF patients 12 years of age and older (Trials 1 and Trial 2) [see Clinical Studies (14)]. In these studies, 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/ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)].

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

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 also 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).

**14.3 Treatment-Related Adverse Reactions**

The most common treatment-related adverse reactions (incidence ≥ 5%) were gastrointestinal (GI) in patients taking TRIKAFTA and placebo. The most common GI adverse reactions were nausea, abdominal pain, diarrhea, vomiting, weight gain, and constipation.

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

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**14.5 Drug Interactions**

The efficacy of TRIKAFTA in patients with CF 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.

**12 CLINICAL PHARMACOLOGY**

Eighty percent of subjects were White; 45% were Black or African American; 11% were Hispanic or Latino; 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); 46% had baseline NS3 resistance-associated substitutions.

Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR in 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. 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)].

**14.6 Treatment of Patients with At Risk of Experiencing or Developing Resistance**

Patients in Trials 1 and 2 who were homozygous for the F508del mutation were randomized to the immediate treatment group or intensive PK group and 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; 11% were Hispanic or Latino; 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).

**14.7 Use in Specific Populations**

**14.7.1 Geriatric Use**

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.

**14.7.2 Pregnancy**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**14.7.3 Women of Childbearing Potential**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**14.8 Reproduction**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**14.9 Nursing Mothers**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**14.10 Patient Counseling**

TRIKAFTA is not effective in 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.

**15 ADVERSE REACTIONS**

**15.1 Clinical Trials Experience**

The safety and effectiveness of TRIKAFTA in the treatment of CF in pediatric patients 12 years and older who have at least one F508del mutation in the CFTR gene has been established. Use of TRIKAFTA for this indication was supported by evidence from two adequate and well-controlled studies in CF patients 12 years of age and older (Trials 1 and Trial 2) [see Clinical Studies (14)].

**15.2 Postmarketing Experience**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**15.3 Laboratory Test Changes**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**15.4 Other Interaction Potentials**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**15.5 Other Important Information**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

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**15.8 Treatment of Patients with At Risk of Experiencing or Developing Resistance**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**15.9 Use in Specific Populations**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.

**15.10 Patient Counseling**

Although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)], the safety and effectiveness of TRIKAFTA in patients with CF aged younger than 12 years of age have not been established.
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| 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 | 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)]. Limitations of Use:
- Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect [see Clinical Studies (14)].
- A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) [see Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION
2.1 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)].

2.2 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 84 mg 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)]. [See Table 2]

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 (8.1)]
  - Mild hepatic impairment and taking a strong or moderate CYP3A 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)]
  - Any degree of hepatic impairment [see Use in Specific Populations (8.7)]

- PMs
  - Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)]
  - Any degree of hepatic impairment [see Use in Specific Populations (8.7)]

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
Co-administration 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)].

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

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

### 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 204 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-∞). 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 AUC0-24h 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]

**Distribution**

Administration of CERDELGA with a high fat meal (approximately 1500 calories with 50% calories from fat) resulted in a 15% decrease in Cmax (not clinically significant) but no change in AUC.

**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 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 hepatic 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 (CV%) of 139% 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]

No clinically significant pharmacokinetic changes were observed for eliglustat when coadministered with intravenous rifampin (an OATP inhibitor), or gastric pH modifying drugs (e.g., aluminum hydroxide, magnesium hydroxide, calcium carbonate, pantoprazole).

In vitro, eliglustat is a substrate of P-glycoprotein (P-gp). The effect of P-gp inhibitors on eliglustat pharmacokinetics is unknown.

**Effect of CERDELGA on other drugs**

**CYP2D6 substrates**

- Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage), metoprolol (a CYP2D6 substrate) mean Cmax and AUC increased by 1.7-fold and 2.3-fold in CYP2D6 EMs, respectively, and by 1.2-fold and 1.6-fold in IMs, respectively [see Drug Interactions (7.2)].
- No dosage adjustment is recommended in patients with mild hepatic impairment taking:
  - a weak CYP2D6 inhibitor
  - a strong, moderate, or weak CYP3A inhibitor

**P-gp substrates**

- Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage) in CYP2D6 EMs and IMs, or 84 mg twice daily in PMs, digoxin (a P-gp substrate) mean Cmax increased by 1.7-fold and AUC increased by 1.5-fold [see Drug Interactions (7.2)].

### 14 CLINICAL STUDIES

They CERDELGA treatment group was comprised of IM (5%), EM (80%) and URM (5%) patients. (...)
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<td>Elosulfase</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>
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<tr>
<td><strong>022291, 04/29/2020</strong></td>
<td>Eltrombopag (1)</td>
<td>Hematology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Risk of Acute Respiratory Complications Patients with acute febrile or respiratory illness at the time of Vimizim infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient’s clinical status prior to administration of Vimizim and consider delaying the Vimizim infusion. Sleep apnea is common in MPS IVA patients. Evaluation of airway patency should be considered prior to initiation of treatment with Vimizim. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an acute reaction, or extreme drowsiness/sleep induced by antihistamine use.</td>
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<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>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).</td>
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<td><strong>022291, 04/29/2020</strong></td>
<td>Eltrombopag (3)</td>
<td>Hematology</td>
<td>Chromosome 7</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Cytogenetic 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. (…) In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported on the therapy, including 5 patients who had complex changes in chromosome 7.</td>
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<tr>
<td><strong>022291, 04/29/2020</strong></td>
<td>Eltrombopag (4)</td>
<td>Hematology</td>
<td>Chromosome 13</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Cytogenetic Abnormalities</td>
</tr>
</tbody>
</table>

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**Last Updated: 12/2020**

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<thead>
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<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>761107, 11/20/2018</td>
<td>Emapalumab-lzsg</td>
<td>Hematology</td>
<td>PRF1, RAB27A, SH2D1A, STXBP2, STX11, UNC13D, XIAP (Hemophagocytic Lymphohistiocytosis)</td>
<td>Clinical Studies</td>
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<td>In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M8 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. (…)</td>
</tr>
<tr>
<td>209608, 09/27/2019</td>
<td>Enasidenib</td>
<td>Oncology</td>
<td>IDH2</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td></td>
<td>1.1 Acute Myeloid Leukemia</td>
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<td>IDHIFA 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.</td>
</tr>
<tr>
<td>210498, 04/08/2020</td>
<td>Encorafenib (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>1 INDICATIONS AND USAGE</td>
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<tr>
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<td></td>
<td>1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma</td>
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<td>BRAF/TV is indicated, in combination with binimetinib, 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)).</td>
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<td>1.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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<td>BRAF/TV is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy (see Dosage and Administration (2.1)).</td>
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<td>1.3 Limitations of Use</td>
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<td></td>
<td>BRAF/TV is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC (see Warnings and Precautions (5.2)).</td>
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<td></td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection</td>
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<td></td>
<td>BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma</td>
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<td></td>
<td>Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAF/TV (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>. BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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Confirms 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: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

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. 2.3 Recommended Dosage for BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

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.

2.4 Recommended Dosage for BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) 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.

2.5 Dosage Modifications for Adverse Reactions

If binimetinib is withheld, reduce BRAFTOVI to a maximum dose of 300 mg (four 75 mg capsules) once daily until binimetinib is resumed [see Warnings and Precautions (5.7)]. Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 1.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) When discontinuation of BRAFTOVI is required, discontinue cetuximab. Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 2.

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma and BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 3.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur with BRAFTOVI. (…)

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 BRAFTOVI [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 BRAFTOVI in combination with binimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS). (…)

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) The safety of BRAFTOVI 300 mg once daily 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). (…)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Of the 698 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib were observed in elderly patients as compared to younger patients [see Clinical Pharmacology (12.3)].

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. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg. After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 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

BRAFTOVI in combination with binimetinib 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. (…)

14.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

BRAFTOVI 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 RQq polymerase chain reaction (PCR) kit with disease progression after 1 or 2 prior regimens. (…)
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<table>
<thead>
<tr>
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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>210496, 04/08/2020</td>
<td>Encorafenib (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Dosage and Administration, Warnings and Precautions, Clinical Studies</td>
<td>2 DOSAGE AND ADMINISTRATION 2.5 Dosage Modifications for Adverse Reactions BRAF V600E or V600K Mutation-Positive Metastatic Melanoma and BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) Dosage modifications for adverse reactions associated with BRAF/TOVI are presented in Table 3.</td>
</tr>
<tr>
<td>761137, 12/18/2019</td>
<td>Entrectinib (1)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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.</td>
</tr>
<tr>
<td>212725, 08/15/2019</td>
<td>Entrectinib (1)</td>
<td>Oncology</td>
<td>ROS1</td>
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</tbody>
</table>

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<td><strong>1 INDICATIONS AND USAGE</strong></td>
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<tr>
<td><strong>1.2 NTRK Gene Fusion-Positive Solid Tumors</strong></td>
<td>Entrectinib (2)</td>
<td>Oncology</td>
<td>NTRK</td>
<td>Indications and Usage, Dosage, Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>Efficacy was assessed in 51 patients with ROS1-positive NSCLC. The median age was 53 years (range: 27 to 72); female (67%); White (57%), Asian (37%), and Black (6%); and Hispanic or Latino (3.6%); never smoked (57%); and ECOG performance status 0 or 1 (88%). Ninety-five percent of patients had metastatic disease, including 43% with CNS metastases; 94% had adenocarcinoma; 69% received prior platinum-based chemotherapy for metastatic or recurrent disease or had progressed in less than 6 months following adjuvant or neoadjuvant therapy. ROS1 positivity was determined by NGS in 71% and by FISH in 29%. Fifty-five percent had central laboratory confirmation of ROS1 positivity using an analytically validated NGS test. (See Table 7)</td>
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<td><strong>2 DOSAGE AND ADMINISTRATION</strong></td>
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<tr>
<td><strong>2.1 Patient Selection</strong></td>
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<tr>
<td>Select patients for treatment of locally advanced or metastatic solid tumors with ROZLYTREK based on the presence of a NTRK gene fusion. (See Clinical Studies (14.2).) An FDA-approved test for the detection of NTRK gene fusion in solid tumors is not available.</td>
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<tr>
<td><strong>2.3 Recommended Dosage for NTRK Gene Fusion-Positive Solid Tumors</strong></td>
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<tr>
<td>Adults The recommended dosage of ROZLYTREK in adults is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity.</td>
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<tr>
<td><strong>6 ADVERSE REACTIONS</strong></td>
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<tr>
<td><strong>6.1 Clinical Trial Experience</strong></td>
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<td>(…) 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. (…)</td>
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<td><strong>8 USE IN SPECIFIC POPULATIONS</strong></td>
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<td><strong>8.4 Pediatric Use</strong></td>
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<tr>
<td>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.</td>
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<tr>
<td><strong>12 CLINICAL PHARMACOLOGY</strong></td>
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<td><strong>12.3 Pharmacokinetics</strong></td>
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<td>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. (…)</td>
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<tr>
<td><strong>14 CLINICAL STUDIES</strong></td>
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<tr>
<td><strong>14.2 NTRK Gene Fusion-Positive Solid Tumors</strong></td>
<td>Entrectinib (2)</td>
<td>Oncology</td>
<td>NTRK</td>
<td>Indications and Usage, Dosage, Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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, STARTRK-1 (NCT02097810) and STARTRK-2 (NCT02568267). 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 6 months of follow-up after the first dose of ROZLYTREK; and no prior therapy with a TRK inhibitor. Patients received ROZLYTREK at various doses and schedules (94% received ROZLYTREK 900 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. (…) (…) 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 57 years (range: 21 to 83); female (59%); White (80%), Asian (13%) and Hispanic or Latino (7%); and ECOG performance status 0 (43%) or 1 (48%). 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). Thirty-four patients (63%) 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. (See Tables 8, 9, and 10)</td>
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<tr>
<td>212018, 04/12/2019</td>
<td>Erdafitinib (2)</td>
<td>Oncology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>• susceptible FGFR3 or FGFR2 genetic alterations, and • progressed during or following at least one line of 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)].</td>
</tr>
</tbody>
</table>

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection
Select patients for the treatment of locally advanced or metastatic urothelial carcinoma with BALVERSA based on the presence of susceptible FGFR genetic alterations in tumor specimens as detected by an FDA-approved companion diagnostic [see Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of FGFR genetic alterations in urothelial cancer is available at: http://www.fda.gov/CompanionDiagnoses.

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 safety of BALVERSA was evaluated in the BLC2001 study that included 87 patients with locally advanced or metastatic urothelial carcinoma which had susceptible FGFR3 or FGFR2 genetic alterations, and which progressed during or following at least one line of prior chemotherapy including within 12 months of neoadjuvant or adjuvant chemotherapy [see Clinical Studies (14.1)]. Patients were treated with BALVERSA at 8 mg orally once daily; with a dose increase to 9 mg in patients with phosphate levels <5.5 mg/dL on Day 14 of Cycle 1. Median duration of treatment was 5.3 months (range: 0 to 17 months). (…)

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma with Susceptible FGFR Genetic Alterations
Study BLC2001 (NCT02365587) was a multicenter, open-label, single-arm study to evaluate the efficacy and safety of BALVERSA in patients with locally advanced or metastatic urothelial carcinoma (mUC). Fibroblast growth factor receptor (FGFR) mutation status for screening and enrollment of patients was determined by a clinical trial assay (CTA). The efficacy population consists of a cohort of eighty-seven patients who were enrolled in this study with disease that had progressed on or after at least one prior chemotherapy and that had at least 1 of the following genetic alterations: FGFR3 gene mutations (R248C, S249C, G370C, Y373C) or FGFR gene fusions (FGFR3-TACC3, FGFR3 BAIA2P2L1, FGFR2-BICC1, FGFR2-CASP7), as determined by the CTA performed at a central laboratory. Tumor samples from 69 patients were tested retrospectively by the Qiagen therascreen® FGFR RQG RT-PCR Kit, which is the FDA-approved test for selection of patients with mUC for BALVERSA. (See Table 6) (…) 

17 PATIENT COUNSELING INFORMATION
Advises the patient to read the FDA-approved patient labeling [Patient Information]. FGFR genetic alterations: Advise patients that evidence of a susceptible FGFR3 or FGFR2 mutation or gene fusion within the tumor specimen is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)].

201532, 10/19/2016

Eribulin (1) | Oncology | ERBB2 (HER2) | Clinical Studies | 14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer
(…) Randomization was stratified by geographic region, HER2/neu status, and prior capecitabine exposure. HALAVEN was administered at a dose of 1.4 mg/m2 on Days 1 and 8 of a 21-day cycle. HALAVEN-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), and 3% hormonal therapy. The main efficacy outcome was overall survival. (…) (…) 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 6 cycles of chemotherapy. (…) 

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<td>021743, 10/18/2016</td>
<td>Erlotinib</td>
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<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<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></td>
<td>Limitations of use:</td>
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<td></td>
<td></td>
<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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<tr>
<td>062759</td>
<td>Erythromycin and Sulfisoxazole</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions</td>
<td>7 DRUG INTERACTIONS</td>
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<td>021323, 01/11/2019</td>
<td>Escitalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug interactions</td>
<td>7.19 Drugs Metabolized by Cytochrome P450 2D6</td>
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<td>021323, 01/11/2019</td>
<td>Escitalopram (2)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Adverse Reactions</td>
<td>In vitro studies did not reveal an inhibitory effect of escitalopram 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 escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. (…)</td>
</tr>
<tr>
<td>022101, 06/07/2018</td>
<td>Esomeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways (…) Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Esomeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John’s Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John’s Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers (Cmax and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (Cmax and AUC decreased by 49.6 % and 43.9%, respectively). Avoid concomitant use of St. John’s Wort or rifampin with NEXIUM.</td>
</tr>
<tr>
<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (1)</td>
<td>Gynecology</td>
<td>PROC</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS BLUVA (estradiol and progesterone) capsules. 1 mg/100 mg, are contraindicated in women with any of the following conditions: • Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders</td>
</tr>
<tr>
<td>210132, 10/29/2018</td>
<td>Estradiol and Progesterone (2)</td>
<td>Gynecology</td>
<td>PROS1</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS BLUVA (estradiol and progesterone) capsules. 1 mg/100 mg, are contraindicated in women with any of the following conditions: • Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders</td>
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<tr>
<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (3)</td>
<td>Gynecology</td>
<td>SERPIN1C1 (Antithrombin III)</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS BLUVA (estradiol and progesterone) capsules. 1 mg/100 mg, are contraindicated in women with any of the following conditions: • Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders</td>
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<td>206488, 10/11/2018</td>
<td>Eteplirsen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE EXONDYS 51 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 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see Clinical Studies (14)]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.</td>
</tr>
<tr>
<td>022254, 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</td>
<td>1 INDICATIONS AND USAGE 1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer 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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| 02/2334, 02/13/2020                   | Everolimus (2) | Oncology | ESR (Hormone Receptor) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 2.2 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer  
The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.  

5 WARNINGS AND PRECAUTIONS  
5.7 Geriatric Patients  
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 < 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 < 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)]. (…)  

6 ADVERSE REACTIONS  
6.1 Clinical Study Experience  
Hormone Receptor-Positive, HER2-Negative Breast Cancer  
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. (…)  

Topical Prophylaxis for Stomatitis  
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. (…)  

8 USE IN SPECIFIC POPULATIONS  
Other Indications  
The safety and effectiveness of AFINITOR/AFINITOR DISPERS2 in pediatric patients have not been established in:  
• Hormone receptor-positive, HER2-negative breast cancer (…)  

12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
(…) The coadministration of AFINITOR with exemestane increased exemestane Cmin by 45% and C2h by 64%; however, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination. (…)  

14 CLINICAL STUDIES  
14.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer  
A randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Table 20 and Figure 1). (…)  

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<td>020753, 05/18/2018</td>
<td>Exemestane</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Adjuvant Treatment of Postmenopausal Women AROMASIN is indicated for adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy (see Clinical Studies (14.1)). (…) 2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dose The recommended dose of AROMASIN in early and advanced breast cancer is one 25 mg tablet once daily after a meal. • adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy (see Clinical Studies (14.1)). (…) 14 CLINICAL STUDIES 14.1 Adjuvant Treatment in Early Breast Cancer The Intergroup Exemestane Study 031 (IES) was a randomized, double-blind, multinational study comparing exemestane (25 mg/day) vs. tamoxifen (20 or 30 mg/day) in postmenopausal women with early breast cancer. (See Table 5) (…) (…) In the hormone receptor-positive subgroup representing about 85% of the trial patients, disease-free survival was also statistically significantly improved (HR = 0.65, 95% CI: 0.53, 0.79, P = 0.00001) in the AROMASIN arm compared to the tamoxifen arm. Consistent results were observed in the subgroups of patients with node negative or positive disease, and patients who had or had not received prior chemotherapy. (See Table 9) (…)</td>
</tr>
<tr>
<td>761139, 12/20/2019</td>
<td>Fam-Trastuzumab Deruxtecan-nxki</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior HER2-based regimens in the metastatic setting. 5 WARNINGS AND PRECAUTIONS 5.1 Interstitial Lung Disease/Pneumonitis Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU [see Adverse Reactions (6.1)]. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. (…) 5.2 Neutropenia Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. (…) 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. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. (…)</td>
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| Fesoterodine, 11/2/2017                | Urology | CYP2D6 | Drug Interactions, Clinical Pharmacology | 6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(….) 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 (NCT02594900). ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31). (…) |
| 7 DRUG INTERACTIONS
7.2 CYP3A4 Inhibitors
Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and diltiazem.

Coadministration of the potent CYP3A4 inhibitor ketoconazole with fesoterodine led to approximately a doubling of the maximum concentration (Cmax) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl tolterodine (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)]. (…) |
| 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 1.8- and 2.5-fold, respectively. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors. |
| 12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The administration of multiple doses of ENHERTU (6.4 mg/kg every 3 weeks, which is 1.2 times the recommended dosage) did not show large mean effect (i.e. >20 ms) on the QTc interval in an open label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer. |
| 14 CLINICAL STUDIES
14.1 Metastatic Breast Cancer
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. (…) |

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| 022526, 08/18/2015 | Flibanserin (1) | Gynecology | CYP2C9 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics
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. CYP2C9 Poor Metabolizers
A study comparing fibanserin exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C9 inhibitor. In 8 women who were poor metabolizers of CYP2C9, Cmax and AUC0-inf of fibanserin 100 mg once daily decreased 23% and 18%, compared to exposures among 8 extensive metabolizers of CYP2C9. |
| 022526, 08/18/2015 | Flibanserin (2) | Gynecology | CYP2C19 | Adverse Reactions, Use in Specific Populations, Clinical Pharmacology | 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 fibanserin exposure compared to CYP2C19 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C19 extensive metabolizers [see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)]. |
| 022526, 08/18/2015 | Flibanserin (3) | Gynecology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics
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. CYP2D6 Poor Metabolizers
A study comparing fibanserin exposure in CYP2D6 poor 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 fibanserin 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. |
| 020985, 12/16/2003 | Fluorouracil (1) | Dermatology | DPYD | Contraindications, Warnings | CONTRAINDICATIONS
(…) Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. (…) WARNINGS
The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive. |

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| 012209, 07/29/2016 | Fluorouracil (2) | Oncology | DPYD | Warnings and Precautions, Patient Counseling Information | 5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity

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 severity, 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.

Withhold 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.

17 PATIENT COUNSELING INFORMATION

Advises:

- Patients to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity, they are at an increased risk of severe and life-threatening mucositis, diarrhea, neutropenia and neurotoxicity [see Warnings and Precautions (5.1)]. (...)

| 020101, 01/30/2009 | Fluoxetine | Psychiatry | CYP2D6 | Precautions, Clinical Pharmacology | PRECAUTIONS

Drug Interactions

Drugs metabolized by CYP2D6: Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coinadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, 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. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (see CONTRAINDICATIONS and WARNINGS).

CLINICAL PHARMACOLOGY

Clinical issues related to metabolism/elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine’s clinical use.

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 enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-fluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among individuals who are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-fluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. (...)

| 018766, 05/09/2016 | Flurbiprofen | Rheumatology | CYP2C9 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Poor Metabolizers of CYP2C9 Substrates

In 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 and phenytoin), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.

| 018554, 07/23/2001 | Flutamide | Oncology | G6PD | Warnings | 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 (e.g., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methemoglobin levels should be considered.

| 020207, 05/29/2019 | Formoterol (1) | Pulmonary | CYP2D6 | Clinical Pharmacology | 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.

| 020207, 05/29/2019 | Formoterol (2) | Pulmonary | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

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|----------------------------------------|------|---------------------|--------------|------------------|----------------
| 02/0450, 10/31/2017                    | Fosphenytoin | Neurology | HLA-B | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
|                                        |      |                     |              |                  | 5.4 Serious Dermatologic Reactions
|                                        |      |                     |              |                  | Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin (the active metabolite of CEREBYX) treatment. 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 SJS/TEN, 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 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.5)].
|                                        |      |                     |              |                  | 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. Consideration should be given to avoiding CEREBYX as an alternative for carbamazepine patients positive for HLA-B*1502.
|                                        |      |                     |              |                  | The use of HLA-B*1502 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 level of dermatologic monitoring have not been studied. |
| 02/2033, 01/04/2017                    | Fluvoxamine | Psychiatry | CYP2D6 | Drug Interactions | 7 DRUG INTERACTIONS
|                                        |      |                     |              |                  | 7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes
|                                        |      |                     |              |                  | (…) 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 altered 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 isoenzyme (e.g., quinidine). (…)
| 02/1344, 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
|                                        |      |                     |              |                  | 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. (…)
|                                        |      |                     |              |                  | 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. (…)
|                                        |      |                     |              |                  | 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 patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy who received at least one dose of FASLODEX plus ribociclib or placebo in MONALEESA-3. Median duration of treatment was 15.8 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (…)
|                                        |      |                     |              |                  | 14 CLINICAL STUDIES
|                                        |      |                     |              |                  | Comparison of FASLODEX 500 mg and Anastrozole 1 mg (FALCON)

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<tr>
<td>021344, 05/13/2020</td>
<td>Fulvestrant (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>A randomized, double-blind, double-dummy, multi-center study (FALCON, NCT01602380) of FASLODEX 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-positive, HER2-negative locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy. (…)</td>
</tr>
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**1 INDICATIONS AND USAGE**

**6.1 Clinical Trials Experience**

**6.2 Adverse Reactions**

**12.2 Pharmacodynamics**

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| 021169, 02/14/2017                     | Galantamine | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

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 isoenzymes 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 3 H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 38-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-95% 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 AUC24h and Cmin. 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-proportionality is observed for AUC∞ increase of unchanged galantamine compared to extensive metabolizers. A total of 356 patients with Alzheimer’s disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

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 as detected by an FDA-approved test [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/CompanionDiagnostics.

14 CLINICAL STUDIES
Non-Small Cell Lung Cancer (NSCLC)
Study 1
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<tr>
<td>206995, 08/22/2018</td>
<td>Gefitinib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>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 106 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, L861Q, or G719X substitution mutation and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. Tumor samples from 67 patients were tested retrospectively using the therascreen® EGFR RQ Kit. 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 the 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 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>
</tr>
<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>
<td>The efficacy and 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. (…)</td>
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| 211349, 05/29/2019                    | Glititinib | Oncology | FLT3 | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Relapsed or Refractory Acute Myeloid Leukemia  
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. |
| 212194, 11/20/2019                    | Givosiran | Gastroenterology | CPOX, HMBS, PPOX (Acute Hepatic Porphyria) | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Newly-Diagnosed CD33-positive AML  
Study ALFA-0701  
(…) 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 ALFA-19  
(…) 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 10^9/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 235/237 (99%) patients; 10% had CD33 expression less than 20%. (…) |
| 02/04/18, 12/21/2018                 | Glimepiride | Endocrinology | G6PD | Warnings and Precautions, Adverse Reactions | 5 WARNINGS AND PRECAUTIONS  
5.3 Hemolytic Anemia  
Sulfonlureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea 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)]. |

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| 017783, 08/18/2016                     | Glibizide | Endocrinology | G6PD | Precautions | The following adverse reactions have been identified during post-approval use of AMARYL. 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. (…)
- Hemolytic anemia in patients with and without G6PD deficiency [see Warnings and Precautions (5.3)] (…)|
| 020051, 08/22/2017                     | Glyburide | Endocrinology | G6PD | Precautions | Hemolytic Anemia
Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonlurea agents can lead to hemolytic anemia. Because GLUCOTROL 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. |
| 211975, 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. |
| 019276, 02/12/2015                     | Goserelin | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.5 Advanced Breast Cancer
ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.
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)]. |
| 020077, 03/12/2019                     | Hydralazine | Cardiology | Nonspecific (NAT) | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.1 Pharmacokinetics
Absorption
(…) 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 28%, 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 saturating first pass metabolism. (…) Metabolism
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. (…) |

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| 009768, 01/27/2017 |                       | Hydroxychloroquine | Infectious Diseases | G6PD | Precautions, Adverse Reactions | PRECAUTIONS
(…) PLAQUEVINIL should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…) ADVERSE REACTIONS
Blood and lymphatic system disorders: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…) |
| 205552, 04/21/2020 |                       | Ibrutinib (1) | Oncology | Chromosome 17p | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion
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)). |
| 205552, 04/21/2020 |                       | Ibrutinib (2) | Oncology | Chromosome 11q | Clinical Studies | 14 CLINICAL STUDIES
14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma
RESONATE
(…) Thirty-two percent of patients had 17p deletion. (…) CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE
The trial enrolled 217 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)
6-Month Follow-Up
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 and 6.2 months [95% CI (4.6, 8.1)] 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. | |
| 205552, 04/21/2020 |                       | Ibrutinib (3) | Oncology | MYD88 | Clinical Studies | 14 CLINICAL STUDIES
14.3 Waldenström’s Macroglobulinemia
INOVADE
(…) 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. (…) |
| 022192, 02/23/2017 |                       | Biperiden | Psychiatry | CYP2D6 | Dosage and Administration, Warnings and Precautions | 2 DOSAGE AND ADMINISTRATION
2.2 Dosage in Special Populations
Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6 | |

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Table of Pharmacogenomic Biomarkers in Drug Labeling

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<td>Oncology</td>
<td>KIT</td>
<td>Precautions, Drug Interactions, Clinical Pharmacology</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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</tbody>
</table>

5 WARNINGS AND PRECAUTIONS
5.3 QT Prolongation
(…) 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)]. (…) |

7 DRUG INTERACTIONS
7.1 Potential for Other Drugs to Affect FANAPT
Fluoxetine: Co-administration 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 P95 by about 2- to 3-fold, and decreased the AUC of its metabolite P95 by one-half. (…) |

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
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 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, P88 and P95. The iloperidone metabolite P95 represents 47.5% 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% - 8% 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. Co-administration 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 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.

2 DOSAGE AND ADMINISTRATION
2.7 Adult Patients with ASM

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-PDGFRα, 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.

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 PDGFRα 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 PDGFRα protein tyrosine kinases. (…) 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. (…) Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

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| 021588, 08/21/2018                      | Imatinib (2) | 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 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)

Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.

1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy

Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

1.3 Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia.

1.4 Pediatric patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients with Ph+ CML CP, AP, or BC

The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients with accelerated phase or blast crisis.

2.2 Adult Patients with Ph+ ALL

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

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)...

3 WARNINGS AND PRECAUTIONS

3.1 Fluid Retention and Edema

In a randomized trial in patients 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. (…)

3.2 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 patients in the Gleevec arm and 2.2% of patients in the nilotinib 300 mg bid arm and severe (Grade 4 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 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

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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/mcL) and thrombocytopenia (less than 75,000/mcL) in the 92 patients with Ph+ ALL compared to 65 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 that included 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 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The safety profile in 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 leukopenia, neutropenia, lymphopenia, and anemia.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

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.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Pediatric Use

(…) 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.

14 CLINICAL STUDIES

14.1 Chronic Myeloid Leukemia

Chronic Phase, Newly Diagnosed

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) (…) (…) 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) (…) (…) 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). (…) 14.2 Pediatric CML

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. (…)  

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| 021588, 08/21/2018 | Imatinib | Oncology | PDGFRB | Indications and Usage, Dosage and Administration, Clinical Studies | (…) 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. 14.3 Acute Lymphoblastic Leukemia 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. 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 MCyR was 2.3 months. (See Table 21) (…) 14.4 Pediatric ALL 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 protocol. 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. (…) (…) 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. (…)
| 021588, 08/21/2018 | Imatinib | Oncology | FIP1L1-PDGFRα | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE 1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD) Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)]. 2 DOSAGE AND ADMINISTRATION 2.6 Adult Patients with MDS/MPD Determine PDGFRα gene rearrangements status prior to initiating treatment. Information on FDA-approved tests for the detection of PDGFRα rearrangements is available at http://www.fda.gov/companiondiagnostics. The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD. 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 Ab1 or PDGFRα 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 Ab1 or PDGFRα 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 Ab1 or PDGFRα protein tyrosine kinases. (…) 14.8 Dermatofibrosarcoma Protuberans Dermatofibrosarcoma Protuberans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22 that results in the fusion of the collagen type 1 alpha 1 gene and the PDGFRα gene. An open-label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients with life-threatening diseases associated with Ab1, Kit or PDGFRα protein tyrosine kinases. (…) 1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL) 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. 2.7 Adult Patients with ASM 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 http://www.fda.gov/companiondiagnostics. |
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2.8 Adult Patients with HES/CEL
The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFβR fusion kinase, 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.

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) (…)

14 CLINICAL STUDIES
14.6 Aggressive Systemic Mastocytosis
(…) Seven of these 20 patients had the FIP1L1-PDGFβR 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 juxtapanel region (one Phe522Cys and one K509R) and four patients had a DB16V c-Kit mutation (not considered sensitive to Gleevec), one with concomitant CML. (See Table 23) (…)

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. (See Table 24) (…)

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| 761040, 08/17/2017                     | Ipilimumab    | Oncology         | BCR-ABL1 (Philadelphia chromosome) | Clinical Studies | 14 CLINICAL STUDIES Patients With Relapsed or Refractory ALL – INO-VATE ALL  
Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. All patients were required to have ≥ 5% bone marrow blasts and to have received 1 or 2 previous induction chemotherapy regimens for ALL. Patients with Philadelphia chromosome-positive B-cell precursor ALL were required to have disease that failed treatment with at least 1 tyrosine kinase inhibitor and standard chemotherapy. (…)  
(…) The median age was 47 years (range: 18-79 years), 276 patients (85%) had Philadelphia chromosome-negative ALL, 206 patients (63%) had a duration of first remission < 12 months, and 55 patients (17%) had undergone a HSCT prior to receiving BESponsa or Investigator’s choice of chemotherapy. (…) |
| 125377, 11/13/2020                     | Ozogamicin    | Oncology         |            | Clinical Studies    | 14 CLINICAL STUDIES  
14.1 Unresectable or Metastatic Melanoma  
The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094863) 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*020101 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  
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, irinotecan, and FOLFOXIRI [see Clinical Studies (14.4)]. This indication is approved under accelerated approval based on overall response rate and duration of response. (…) |
| 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, irinotecan, and FOLFOXIRI [see Clinical Studies (14.4)]. This indication is approved under accelerated approval based on overall response rate and duration of response. (…) |

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with metastatic NSCLC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression [see Clinical Studies (14.6)]. Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnosics.

2.2 Recommended Dosage

The recommended dosages of YERVOY as a single agent are presented in Table 1. (See Table 2)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

(…) Of the 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received YERVOY with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks with in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older [see Clinical Studies (14.6)]. (…)

14 CLINICAL STUDIES

14.3 Previously Untreated Advanced Renal Cell Carcinoma

CHECKMATE-9LA (NCT03215706) was a randomized (1:1), open-label trial in patients with metastatic or recurrent RCC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent RCC (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. (…)

The trial did not demonstrate statistically significant improvement in OS and ORR for patients randomized to YERVOY and nivolumab arm as 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. (…) Of the 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab (n=396) or platinum-doublet chemotherapy (n=197), the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older [see Clinical Studies (14.6)]. (…)

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-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. 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 as 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. (…)

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 RCC. In Combination with Nivolumab and Platinum-Doublet Chemotherapy

CHECKMATE-6LA (NCT02159706) 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 [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. (…)

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 <1% or nonquantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. (…) Patients enrolled in the YERVOY and nivolumab MS-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. Patients enrolled in the single-agent nivolumab MS-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 23) (…)

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<tr>
<td><strong>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 (69%) 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 &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. (…)</strong></td>
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<tr>
<td><strong>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%.</strong></td>
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| 125377, 11/13/2020                     | Ipilimumab     | Oncology        | ALK        | Indications and Usage, Adverse Reactions, Clinical Studies | 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 untreated metastatic 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 IIB (with no in-transit metastases) cutaneous melanoma; to YERVOY 1 mg/kg, administered in combination with nivolumab, in three trials: CHECKMATE214, 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. (…)  

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| 125377, 11/13/2020                    | Ipilimumab (5) | Oncology | EGFR | Indications and Usage, Adverse Reactions, Clinical Studies | 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.

5 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 IIIC (with no in-transit metastases) cutaneous melanoma; to YERVOY 1 mg/kg, administered in combination with nivolumab, in three trials: CHECKMATE214, 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. (…)

14CLINICAL 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-Doublt Chemotherapy
CHECKMATE-816 (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. (…)

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<td>Chromosome 14q;16q</td>
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<td>017624, 04/27/2017</td>
<td>Isoflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
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<td>Isoniazid, Pyrazinamide, and Rifampin</td>
<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
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<td>(…) Isoniazid is metabolized in the liver mainly by acetylation and dehydroxylation. The rate of acetylation is genetically determined. Approximately 50% of African Americans and Caucasians are “slow inactivators” and the rest 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.</td>
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<tr>
<td>019790, 10/24/2014</td>
<td>Isosorbide Dinitrate</td>
<td>Cardiology</td>
<td>CYB5R</td>
<td>OVERDOSAGE</td>
<td>Methemoglobinemia</td>
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<td>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 moiety 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 4.8-8.9 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.</td>
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<tr>
<td>020215, 10/02/2014</td>
<td>Isosorbide Mononitrate</td>
<td>Cardiology</td>
<td>CYB5R</td>
<td>OVERDOSAGE</td>
<td>Methemoglobinemia</td>
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<td>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 moiety of isosorbide mononitrate is 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 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.</td>
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<td>203188, 04/26/2019</td>
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<td>Pulmonary</td>
<td>CFTR</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>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 (14)].</td>
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<td>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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<td>6 ADVERSE REACTIONS</td>
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<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 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)]:</td>
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<td>• 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.</td>
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<td>• 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 G505D, G1244E, G1349D, G178R, G551S, G970R, S549N, S1255P, S549R, or S549R mutation in the CFTR gene. Of 34 patients enrolled, 32 had the G551D mutation and 2 had the S549R mutation.</td>
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<td>• An 8-week, crossover design trial (Trial 7) involving patients between the ages of 12 and 72 years who were homozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 106 patients were randomized to and received KALYDECO.</td>
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<td>• 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).</td>
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| 12.2 Pharmacodynamics | **Sweat Chloride Evaluation**

**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, S549R, or S549R mutation in the CFTR gene (Trial 4), the treatment difference in mean change in sweat chloride from baseline through 24 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 -8, 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 aged 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 for patients aged 12 months to less than 24 months (n=10) was -73.5 mmol/L (95% CI -86.0, -61.0) at Week 24, and the mean absolute change from baseline in sweat chloride for patients aged 6 months to less than 12 months (n=6) was -58.6 mmol/L (95% CI -75.9, -41.3) at Week 24 [see Use in Specific Populations (8.4)]. (…)

### 14 CLINICAL STUDIES

14.1 Trials in Patients with CF who have a G551D Mutation in the CFTR Gene

**Efficacy**

The efficacy of KALYDECO in patients with CF who have a G551D mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving KALYDECO 150 mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study. (…)


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:

- 6 to 17 years of age with a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H mutation in the CFTR gene [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 ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)]. (…)

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, 3272-26A→G, 3849+10kbC→T, 711+3A→G and EB31X 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) vitro in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal). (see Table 3)
## Table of Pharmacogenomic Biomarkers in Drug Labeling

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The safety profile from two pediatric trials in CF patients aged 6 through 11 years who are homozygous for the F508del mutation, a 24-week, open-label trial (Trial 6) in 60 patients aged 2 through 5 years homozygous for the F508del-CFTR mutation. (…) Table 3 shows adverse reactions occurring in ≥5% of lumacaftor/ivacaftor patients in the two double-blind, placebo-controlled, Phase 3 clinical trials, each with 24 weeks of treatment (Trials 1 and 2). In addition, the following adverse reactions were reported: A 24-week, open-label trial (Trial 3) in 58 patients with CF aged 6 through 11 years homozygous for the F508del-CFTR mutation. (…) A 24-week, placebo-controlled trial (Trial 4) in 204 patients aged 6 through 11 years homozygous for the F508del-CFTR mutation. (…) 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 (ppFEV1<40).

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1. The treatment difference from placebo for the mean absolute change in percent predicted FEV1 through Week 16 in patients with CF homozygous for the F508del mutation in the CFTR gene was 1.72 percentage points (1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively) and did not reach statistical significance (Table 6). (See Table 6) (…)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The efficacy of ORKAMBI in children aged 2 through 11 years is extrapolated from efficacy in patients aged 12 years and older homozygous for the F508del mutation in the CFTR gene and who had FEV1 ≥40% predicted. (…) The 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 and 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 adverse reactions were reported: A 24-week, open-label trial (Trial 3) in 58 patients with CF aged 6 through 11 years homozygous for the F508del-CFTR mutation. (…) A 24-week, placebo-controlled trial (Trial 4) in 204 patients aged 6 through 11 years homozygous for the F508del-CFTR mutation. (…) 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 (ppFEV1<40).

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1. The treatment difference from placebo for the mean absolute change in percent predicted FEV1 through Week 16 in patients with CF homozygous for the F508del mutation in the CFTR gene was 1.72 percentage points (1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively) and did not reach statistical significance (Table 6). (See Table 6) (…)

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<td>Pharmacology, Clinical Studies</td>
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</table>

6 ADVERSE REACTIONS

The safety profile of the CF patients enrolled in Trial 2 who were heterozygous 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 Pharmacodynamics

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, multi-cohort trial which included 176 patients with CF (homozygous for the F508del mutation) 18 years of age and older with a screening ppFEV1≥40. In the study, 34 and 106 patients, respectively, received tezacaftor at once-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 sufficiency), 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)

Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean ppFEV1 at baseline was 60.0% (range: 27.8% to 98.2%). (see Table 8 and Figure 2) (…).

14.2 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Predicted to be Responsive to Tezacaftor/ivacaftor (Trial 2)

Trial 2 evaluated 244 patients with CF aged 12 years and older (mean age 34.8 years). The mean ppFEV1 at baseline was 62.2% (range: 34.6 to 93.5). Of the 244 patients included in the efficacy analysis, 146 patients had a splice mutation and 98 patients had a missense mutation as the second allele. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (see Table 9).

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: -0.1, 0.3) compared to placebo. The treatment effect was statistically significant in the subgroup of patients with splice mutations and missense mutations predicted to be responsive to tezacaftor/ivacaftor (see Table 8 and Figure 2) (…).

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 (Trial 3)

Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.3 years) who were heterozygous for the F508del mutation and had a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. CF patients with the F508del mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, 95% CI: (-0.1, 0.3), and 0.3 kg/m2 [95% CI (0.1, 0.5)] versus placebo for the overall, splice, and missense mutation populations of patients, respectively.

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: -0.1, 0.3) compared to placebo. The treatment effect was statistically significant in the subgroup of patients with splice mutations and missense mutations predicted to be responsive to tezacaftor/ivacaftor (see Table 8 and Figure 2) (…).

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<td>211192, 05/02/2019</td>
<td>Ixabepilone (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (EC) 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. (EC) 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 48% of patients. ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%. (EC) Monotherapy HER2-positive patients must also have progressed during or after discontinuation of trastuzumab.</td>
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<tr>
<td>211192, 05/02/2019</td>
<td>Ixabepilone (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (EC) 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. (EC) Monotherapy HER2-positive patients must also have progressed during or after discontinuation of trastuzumab.</td>
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12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics

There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. Results from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=8) of cytochrome P450 (CYP) 2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations and the amount excreted into urine of the O-desmethyl metabolite were about 70% reduced in PMs compared to EMs.

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-Dose Interactions
Clopidogrel
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with PREVACID 30 mg (n=40), for nine days was conducted. (…)

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<td>The safety of TYKERB has been evaluated in more than 12,000 patients in clinical trials. (…)</td>
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<td>Hormone Receptor-Positive, HER2+ Metastatic Breast Cancer: (…)</td>
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<td>In another randomized, Phase 3 clinical trial of postmenopausal patients (N = 355) with hormone receptor positive (HR+), HER2-positive metastatic breast cancer (MBC) which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies patients received TYKERB with trastuzumab and an aromatase inhibitor (AI) (letrozole, exemestane, or anastrozole), TYKERB with an AI, or trastuzumab with an AI. (…)</td>
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<td>Decreases in Left Ventricular Ejection Fraction (…) Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. (…)</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.5 Geriatric Use</td>
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<td>Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capcitabine (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. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 HER2-Positive Metastatic Breast Cancer</td>
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<td>The efficacy and safety of TYKERB in combination with capcitabine 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. (…)</td>
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<td>Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (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. (…) (…)</td>
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<td>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 capcitabine relative to trastuzumab in combination with capcitabine in women with HER2-positive metastatic breast cancer (N = 540). (…)</td>
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<td>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). (…)</td>
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<td>14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer</td>
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<td>The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,288 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-negative 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)</td>
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<td>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. (…)</td>
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<th>Labeling Text‡</th>
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</table>
| 022059, 12/06/2018                     | Lapatinib (3) | Oncology          | HLA-DQA1   | Clinical Pharmacology | **12 CLINICAL PHARMAOCOLOGY**
|                                        |               |                   |            |                   | 12.5 Pharmacogenomics |
|                                        |               |                   |            |                   | The HLA alleles DOA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DOA1*02:01 or DRB1*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 genotypy. (…)
|                                        |               |                   |            |                   | **12.5 Pharmacogenomics** |
|                                        |               |                   |            |                   | The HLA alleles DOA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DOA1*02:01 or DRB1*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 genotypy. (…)

| 022059, 12/06/2018                     | Lapatinib (4) | Oncology          | HLA-DRB1   | Clinical Pharmacology | **12 CLINICAL PHARMAOCOLOGY**
|                                        |               |                   |            |                   | 12.5 Pharmacogenomics |
|                                        |               |                   |            |                   | The HLA alleles DOA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DOA1*02:01 or DRB1*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 genotypy. (…)

| 210861, 11/26/2018                     | Larotrectinib | Oncology          | NTRK       | Indications and Usage, Dosage and | **1 INDICATIONS AND USAGE**
|                                        |               |                   |            |                   | VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that: * have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, (…

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<tr>
<td><strong>205834, 11/09/2017</strong></td>
<td>Ledipasvir and Sofosbuvir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td><strong>Clinical Studies</strong></td>
<td><strong>14 CLINICAL STUDIES</strong></td>
</tr>
<tr>
<td><strong>14.2 Clinical Trials in Subjects with Genotype 1 HCV</strong></td>
<td>Treatment-Naïve Adults without Cirrhosis — ION-1 (Study 0108)</td>
<td>$(\ldots)$</td>
<td>Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated subjects, the median age was 55 years (range: 20 to 75); 58% of the subjects were male; 78% were White; 12% were Black; 95% were Hispanic or Latino; mean body mass index was 26.0 kg/m² (range: 18.0 to 66.0 kg/m²); 85% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 80% had genotype 1a HCV infection; 73% had non-C/C IL28B alleles (CT or TT). $(\ldots)$</td>
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</tr>
<tr>
<td><strong>14.4 Clinical Trials in Subjects with Genotype 1 HCV</strong></td>
<td>Treatment-Naïve Adults with or without Cirrhosis — ION-1 (Study 0102)</td>
<td>$(\ldots)$</td>
<td>Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated subjects, the median age was 55 years (range: 20 to 75); 58% of the subjects were male; 78% were White; 12% were Black; 95% were Hispanic or Latino; mean body mass index was 26.0 kg/m² (range: 18.0 to 66.0 kg/m²); 85% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 80% had genotype 1a HCV infection; 73% had non-C/C IL28B alleles (CT or TT). $(\ldots)$</td>
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<tr>
<td><strong>14.14 Clinical Trials in Subjects Coinfected with HCV and HIV-1</strong></td>
<td>Previously-Treated Adults with or without Cirrhosis — ION-2 (Study 0109)</td>
<td>$(\ldots)$</td>
<td>Demographics and baseline characteristics were balanced across the treatment groups. Of the 440 treated subjects, the median age was 57 years (range: 24 to 75); 65% of the subjects were male; 81% were White; 18% were Black; 96% were Hispanic or Latino; mean body mass index was 26.0 kg/m² (range: 20.0 to 56.0 kg/m²); 85% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 79% had genotype 1a HCV infection; 79% had non-C/C IL28B alleles (CT or TT); and 16% had cirrhosis. $(\ldots)$</td>
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</tr>
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</table>

**201880, 05/28/2019**

Lanctomamide | Hematology | Chromosome 5q | **BOXED WARNING** | WARNINGS: 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 or reduction during the major study. Thirty-four percent of patients had to have a second dose delay or 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)].

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<tr>
<td>206947, 02/20/2020</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 1.2 Myelodysplastic Syndromes 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>
</tr>
<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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</table>
| 020728, 04/05/2018 | Letrozole | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Studies | 1.1 INDICATIONS 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.
| | | | | | Femara is indicated for first-line 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.
| | | | | | 6 AVERSE 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<0.0001).
| | | | | | 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 randomized 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 after 5 years of adjuvant treatment with tamoxifen.
| | | | | | Table 9 shows the study results. Disease-free survival was measured as the time from randomization to the earliest event of loco-regional or distant recurrence of the primary disease or development of contralateral breast cancer or death.
| | | | | | DFS by hormone receptor status, nodal status and adjuvant chemotherapy were similar to the overall results. Data were premature for an analysis of survival.
| | | | | | 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 IIIB) or metastatic breast cancer.
| | | | | | Time to progression (TTP) was the primary endpoint of the trial.
| | | | | | Table 11 shows results in the subgroup of women who had received prior antiestrogen adjuvant therapy.
| | | | | | Table 13 shows results in the subgroup of patients who had previously treated with at least antiestrogen therapy.
| | | | | | 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 antiestrogen therapy.
| | | | | | 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.
| | | | | | 12 CLINICAL PHARMACOLOGY
| | | | | | 12.3 Pharmacokinetics
| 021451, 11/02/2018 | Lidocaine 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.
| | | | | | 12 CLINICAL PHARMACOLOGY
| | | | | | 12.3 Pharmacokinetics
| 021451, 11/02/2018 | Lidocaine 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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| 02/1623, 11/02/2018 Lidoxaine 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. (…)

02/1623, 11/02/2018 Lidoxaine 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.

17 PATIENT COUNSELING INFORMATION
• Advise patients not to use SYNERA if they have a history of methemoglobinemia.
• Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis), headache, rapid heart rate, shortness of breath, lightheadedness, or fatigue. (…)

20/229, 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)].

213969, 11/20/2020 Lonafarnib (1) | Inborn Errors of Metabolism | LMNA | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
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 ZMPSTE24 mutations

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 ZMPSTE24 mutations) have been established in pediatric patients 12 months of age and older. Use of ZOKINVY for these indications is supported by adequate and well controlled studies 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.

8.6 Adult Use

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<tr>
<td>210868, 11/20/2020</td>
<td>Lorlatinib (2)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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 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 (NCT00425607) was a Phase 2 open-label, single-arm trial that evaluated the efficacy of ZOKINVY in 28 patients (20 with classic HGPS, one with non-classic HGPS, and one with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation with progerin-like protein accumulation). (…)</td>
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<tr>
<td>210868, 05/29/2020</td>
<td>Lorlatinib (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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 2 years of age and older. Use of ZOKINVY for these indications is supported by adequate and well controlled studies 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. 8.6 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 2 years of age and older [see Clinical Studies (14)]. 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 2 years of age and older [see Clinical Studies (14)].</td>
</tr>
<tr>
<td>210868, 05/29/2020</td>
<td>Lorlatinib (2)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Adverse Reactions</td>
<td>14.1 ALK-Positive Metastatic NSCLC Previously Treated with an ALK Kinase Inhibitor The efficacy of LORBRENA was demonstrated in a subgroup of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK kinase inhibitors who were enrolled in a non-randomized, dose-ranging and activity-estimating, multi cohort, multicenter study (Study B7461001, NCT01970865). (…) In addition, for patients with ALK-positive metastatic NSCLC, the extent and type of prior treatment was specified for each individual cohort (See Table 4). (…)</td>
</tr>
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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 (NCT00425607) was a Phase 2 open-label, single-arm trial that evaluated the efficacy of ZOKINVY in 28 patients (20 with classic HGPS, one with non-classic HGPS, and one with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation with progerin-like protein accumulation). (…)
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<tr>
<td>214103, 11/23/2020</td>
<td>Lumasiran</td>
<td>Urology</td>
<td>AGXT</td>
<td>1 INDICATIONS AND USAGE</td>
<td>OXLUMO is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients [see Clinical Pharmacology (12.1), Clinical Studies (14.1, 14.2)].</td>
</tr>
</tbody>
</table>
| 761136, 11/08/2019                     | Lusopteceptor-aamt | Hematology | HBB | 14 CLINICAL STUDIES | 14.1  
|                                           | | | | 14.1  
|                                           | | | | 14.1  
|                                           | | | | 14.1  
| 210923, 07/31/2018                     | Lusutrombopag (1) | Hematology | F2 (Prothrombin) | 5 WARNINGS AND PRECAUTIONS | 5.1  
| 210923, 07/31/2018                     | Lusutrombopag (2) | Hematology | F5 (Factor V Leiden) | 5 WARNINGS AND PRECAUTIONS | 5.1  

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<tr>
<td>208700, 05/29/2020</td>
<td>Lu-177 Lutetium Dotatate</td>
<td>Oncology</td>
<td>SSTR (Antithrombin III)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>(...) 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>PROC</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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<td>210923, 07/31/2018</td>
<td>Lusutrombopag (3)</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>
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<td>Hematology</td>
<td>SERPINC1</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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| 019632, 06/00/1998                     | Mafenide | Infectious Diseases | G6PD | Warnings, Adverse Reactions | WARNINGS: Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate. (…)

12.3 Pharmacokinetics

| 761150, 12/16/2020 | Margetuximab (1) | Oncology | ERBβ2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies | MARGETZA 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-HER2 regimens, at least one of which was for metastatic disease [see Dosage and Administration (2.1) and Clinical Studies (14.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of MARGETZA was evaluated in HER2-positive breast cancer patients who received two or more prior anti-HER2 regimens in SOPHIA [see Clinical Studies (14.1)]. (See Tables 1 and 2) (…)

12 CLINICAL PHARMAKOLOGY

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 (21%) µg/day/mL in patients with HER2-positive relapsed or refractory advanced breast cancer. (…)

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 > 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 > 2), number of prior therapy lines (≤ 2 or > 2) or concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine). The effect of severe renal impairment (CLcr 15 to 29 mL/min), and stage renal disease with or without hemodialysis, and moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin >3 ULN and any AST) on margetuximab-cmkb PK is unknown.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

The efficacy of MARGETZA plus chemotherapy was evaluated in SOPHIA (NCT02492711), a randomized, multicenter, open-label trial of 536 patients with IHC 3+ or IGH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized (1:1) to MARGETZA plus chemotherapy or trastuzumab plus chemotherapy.

| 761150, 12/16/2020 | Margetuximab (2) | Oncology | FCGR2A (CD32A) | Clinical Pharmacology | 12 CLINICAL PHARMAKOLOGY

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 > 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 > 2), number of prior therapy lines (≤ 2 or > 2) or concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine). The effect of severe renal impairment (CLcr 15 to 29 mL/min), and stage renal disease with or without hemodialysis, and moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin >3 ULN and any AST) on margetuximab-cmkb PK is unknown.

| 761150, 12/16/2020 | Margetuximab (3) | Oncology | FCGR2B (CD32B) | Clinical Pharmacology | 12 CLINICAL PHARMAKOLOGY

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 > 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 > 2), number of prior therapy lines (≤ 2 or > 2) or concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine). The effect of severe renal impairment (CLcr 15 to 29 mL/min), and stage renal disease with or without hemodialysis, and moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin >3 ULN and any AST) on margetuximab-cmkb PK is unknown.

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<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 ≤ 1.5 ULN and any AST &gt; ULN, or total bilirubin 1 to 1.5 ULN and any AST &gt; ULN), 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), concurrent chemotherapy (capecitabine, 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 &gt; ULN) or severe hepatic impairment (total bilirubin &gt; 3 ULN and any AST &gt; ULN) on margetuximab-cmkb PK is unknown.</td>
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<td>010721, 06/28/2019</td>
<td>Meclizine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.8 Genetic CYP2D6 Polymorphism The genetic polymorphism of CYP2D6 that results in poor-, intermediate-, extensive-, and ultrarapid metabolizer phenotypes could contribute to large inter-individual variability in meclizine exposure. Therefore, when ANTIVERT® is administered to patients with CYP2D6 polymorphism, monitor for adverse reactions and clinical effect accordingly.</td>
</tr>
<tr>
<td>211210, 10/19/2019</td>
<td>Meloxicam</td>
<td>Anesthesiology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.8 Poor Metabolizers of CYP2C9 Substrates In 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 or phenytoin), consider dose reduction, as these patients may have abnormally high plasma levels of meloxicam due to reduced metabolic clearance. Monitor these patients for adverse effects.</td>
</tr>
</tbody>
</table>
| 012250, 11/02/2019                     | Mepivacaine (1) | Anesthesiology | G6PD       | Warnings | 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. (…)
| 012250, 11/02/2019                     | Mepivacaine (2) | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings | 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. (…)
| 205819, 04/09/2020                     | Mercaptopurine (1) | Oncology      | TPMT       | Dosage and Administration, Warnings and Precautions, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION 2.1 Maintenance Therapy 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 Smethyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression. 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 homozgyous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozgyous 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. |

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<td>Dosage and Administration, Warnings and Precautions, Clinical Pharmacology</td>
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## 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 thiorurine 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 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 TPMT 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, 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. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiorurine 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)).

### 12 WARNINGS AND PRECAUTIONS

#### 12.2 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 thiorurine 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

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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 (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%; homogygous 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 TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT<sup>2</sup>, TPMT<sup>3A</sup>, and TPMT<sup>3C</sup> 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 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 5.3 Lack of Effectiveness

Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to a deficiency in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD 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. PROVAYBLUE™ may result in severe hemolysis and anemia. Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with PROVAYBLUE™ may result in severe hemolysis and anemia. PROVAYBLUE™ is contraindicated for use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency [see Contraindications (4)].

5 WARNINGS AND PRECAUTIONS

5.3 Lack of Effectiveness

Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to a deficiency in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD 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.

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5.5 Methemoglobinemia

Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may be fatal [see Overdosage (10)].

5.6 Methemoglobinemia

Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to a deficiency in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD 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.

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5.10 Methemoglobinemia

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5.11 Methemoglobinemia

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5.12 Methemoglobinemia

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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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</table>
| 019662, 05/06/2014                     | Metoprolol | Cardiology  | CYP2D6 | Drug Interactions, Clinical Pharmacology | 2.3 Dosage for Acute and Recurrent Diabetic Gastroparesis
The recommended adult dosage for the treatment of acute and recurrent diabetic gastroparesis 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.
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) |
| 125390, 05/15/2020                     | Metreleptin | Endocrinology | LEP | Contraindications | 8 USE IN SPECIFIC POPULATIONS
8.9 CYP2D6 Poor Metabolizers
Metoclopramide is a substrate of CYP2D6. The elimination of metoclopramide may be slowed in patients who are CYP2D6 poor metabolizers (compared to patients who are CYP2D6 intermediate, extensive, or ultra-rapid metabolizers); possibly increasing the risk of dystonic and other adverse reactions to Reglan [see Clinical Pharmacology (12.3)]. Reduce the Reglan dosage in patients who are poor CYP2D6 metabolizers [see Dosage and Administration (2.2, 2.3)]. |
| 207997, 03/04/2020                     | Midostaurin (1) | Oncology | FLT3 | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Acute Myeloid Leukemia
RYDAPT is indicated, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by a FDA approved test [see Dosage and Administration (2.1), Clinical Studies (14.1)]. (…)
2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of AML with RYDAPT based on the presence of FLT3 mutation positivity [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of FLT3 mutation in AML is available at: http://www.fda.gov/CompanionDiagnostics.
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Acute Myeloid Leukemia
The safety evaluation of RYDAPT (50 mg twice daily with food) in patients with newly diagnosed FLT3 mutated AML is based on a randomized, double-blind, trial of RYDAPT (n=345) or placebo (n=335) with chemotherapy [see Clinical Studies (14.1)]. (…)
Table 3 presents the key laboratory abnormalities from the same randomized trial in patients with newly diagnosed FLT3 mutated AML. (See Table 2) (…)
14 CLINICAL STUDIES |

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<tr>
<td>207997, 03/04/2020</td>
<td>Midostaurin (2)</td>
<td>Oncology</td>
<td>NPM1</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Acute Myeloid Leukemia Study 1 MIDOSTAURIN (2) in combination with chemotherapy was investigated in a randomized, double-blind placebo-controlled trial of 717 patients with newly-diagnosed FLT3-mutated AML. In this study, FLT3 mutation 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 MIDOSTAURIN treatment. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio less than 0.7, and ITD with allelic ratio greater than or equal to 0.7. (…). The randomized patients had a median age of 47 years (range, 18-60 years), 44% were male, and 88% had a performance status of 0-1. AML was de novo in 95%. The percentage of patients with FLT3-ITD allelic ratio &lt; 0.7, FLT3-TKD allelic ratio ≥ 0.7, and FLT3-TKD mutations were identical (per randomized FLT3 stratum) on both arms (48%, 30%, and 23%, respectively). (…).</td>
</tr>
<tr>
<td>207997, 03/04/2020</td>
<td>Midostaurin (3)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Systemic Mastocytosis Study 2 (…) Of the 116 patients treated, a study steering committee identified 89 patients who had measurable C-finding s 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 MIDOSTAURIN by modified Valant criteria for ASM and SM-AHN (Table 7). Table 7 shows responses to MIDOSTAURIN according to modified Valant 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>
</tr>
<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>1 INDICATIONS AND USAGE 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>
</tr>
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<tr>
<td>Mivacurium</td>
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<td>BCHE</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
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<tr>
<td>Mirabegron</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
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</table>

### 14 CLINICAL STUDIES
(….) Of the 67 enrolled patients, 50 patients (32 females, 18 males) had amenable GLA variants based on the in vitro amenable 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.

### 202811, 04/27/2018

- **Mirabegron**
  - **Urology**
  - **CYP2D6**
  - **Clinical Pharmacology**

- **12 CLINICAL PHARMACOLOGY**
  - **12.3 Pharmacokinetics**
  - **Metabolism**

  Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although in vitro studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, in vivo results indicate that these isozymes play a limited role in the overall metabolism. In healthy subjects who are genetically poor metabolizers of CYP2D6, mean Cmax and AUCtau were approximately 16% and 17% higher than in extensive metabolizers of CYP2D6, respectively. In vitro and ex vivo studies have shown the involvement of butylycholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

### 020098, 07/26/2018

- **Mivacurium**
  - **Anesthesiology**
  - **BCHE**
  - **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.

- **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 antineoplastic 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 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 three such adult 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 conventional doses of neostigmine. 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 or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of MIVACRON are not recommended in homozygous patients. MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After an initial dose of 0.15 mg/kg MIVACRON, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotype and normal plasma cholinesterase activity. Lower infusion rates of MIVACRON are recommended in these patients (see PRECAUTIONS - Reduced Plasma Cholinesterase Activity).

### 020717, 01/15/2015

- **Modafinil**
  - **Psychiatry**
  - **CYP2D6**
  - **Clinical Pharmacology**

- **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., desipramine and doxepin) 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 CYP2D6).
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<td>Nefazodone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions, Adverse Reactions</td>
<td>Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS) (\ldots)</td>
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<tr>
<td>014214, 11/28/2012</td>
<td>Nalidixic Acid</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
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<td>Cardiology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>(\ldots)</td>
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<td>Nefazodone</td>
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<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
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<td>(Hormone Receptor)</td>
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<td>14.1 Extended Adjuvant Treatment of Early Stage Breast Cancer</td>
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<td>The safety and efficacy of NERLYNX were investigated in the ExteNET trial</td>
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<td>(NCT00878709), a multicenter, randomized, double-blind, placebo-controlled</td>
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<td>study of NERLYNX after adjuvant treatment with trastuzumab in women with</td>
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<td>HER2-positive breast cancer. The data described below reflect the safety data</td>
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<td>of NERLYNX plus capcitabine in NALA, a randomized, multicenter, multinational,</td>
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<td>open-label, active-controlled study of NERLYNX within 2 years after</td>
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<td>BCR-ABL1</td>
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<td>(Philadelphia</td>
<td>(Chromosome)</td>
<td>Usage, Dosage and</td>
<td>1.1 Adult and Pediatric Patients with Newly Diagnosed Ph+ CML-CP</td>
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<td>chromosome)</td>
<td></td>
<td>Administration,</td>
<td>Tasigna (nilotinib) is indicated for the treatment of adult and pediatric</td>
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<td></td>
<td>Warnings and</td>
<td>patients greater than or equal to 1 year of age with newly diagnosed</td>
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<td></td>
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<td></td>
<td></td>
<td>Precautions,</td>
<td>Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse</td>
<td>phase. Tdasigna is indicated for the treatment of adult patients with chronic</td>
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<td></td>
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<td></td>
<td></td>
<td>Reactions, Use in</td>
<td>phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML)</td>
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<td></td>
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<td></td>
<td>Specific</td>
<td>resistant or intolerant to prior therapy that included imatinib.</td>
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<td>Populations,</td>
<td>1.3 Pediatric Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP</td>
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<td>Clinical</td>
<td>Tasigna is indicated for the treatment of pediatric patients greater than</td>
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<td></td>
<td>Pharmacology,</td>
<td>or equal to 1 year of age with chronic phase Philadelphia chromosome positive</td>
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<td></td>
<td>Clinical Studies</td>
<td>chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior</td>
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<td></td>
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<td></td>
<td>tyrosine-kinase inhibitor (TKI) therapy.</td>
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</table>

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<th>NDA/ANDA/BLA Number,Label Version Date</th>
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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>2.2 Discontinuation of treatment after a sustained molecular response (MR4.5) on Tasigna</td>
<td>Patient Selection</td>
<td>Eligibility for Discontinuation of Treatment</td>
<td>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 $\leq 0.0032$% IS)</td>
<td>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.</td>
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<td>Consider discontinuation of treatment in patients with newly diagnosed Ph+ CML-CP who have:</td>
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<tr>
<td></td>
<td>• been treated with Tasigna for at least 3 years</td>
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<td>• maintained a molecular response of at least MR4.0 (corresponding to $\leq 0.01$% IS) for one year prior to discontinuation of therapy</td>
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<td></td>
<td>• achieved an MR4.5 for the last assessment taken immediately prior to discontinuation of therapy</td>
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<tr>
<td></td>
<td>• been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)</td>
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<td></td>
<td>• no history of accelerated phase or blast crisis</td>
<td></td>
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<tr>
<td></td>
<td>• no history of prior attempts of treatment-free remission discontinuation that resulted in relapse</td>
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<td></td>
<td>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:</td>
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<tr>
<td></td>
<td>• been treated with Tasigna for a minimum of 3 years</td>
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<tr>
<td></td>
<td>• been treated with imatinib only prior to treatment with Tasigna</td>
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<tr>
<td></td>
<td>• achieved a molecular response of MR4.5 (corresponding to $\leq 0.0032$% IS)</td>
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<tr>
<td></td>
<td>• sustained an MR4.5 for a minimum of one year immediately prior to discontinuation of therapy</td>
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<tr>
<td></td>
<td>• been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)</td>
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<td></td>
<td>• no history of accelerated phase or blast crisis</td>
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<td></td>
<td>• no history of prior attempts of treatment-free remission discontinuation that resulted in relapse.</td>
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<td></td>
<td>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)].</td>
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<td>The patient can then proceed to the original monitoring schedule.</td>
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<td>2.3 Reinitiation of treatment in patients who lose molecular response after discontinuation of therapy with Tasigna.</td>
<td>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)].</td>
<td>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.</td>
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<td>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 MR4.0) 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)].</td>
<td>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.</td>
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<td>2.4 Dosage Modification for QT Interval Prolongation</td>
<td>See Table 2 for dose adjustments for QT interval prolongation [see Clinical Pharmacology (12.2)].</td>
<td>(See Table 2)</td>
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<td>2.7 Dosage Modification for Hepatic Impairment</td>
<td>If possible, consider alternative therapies. If Tasigna must be administered to patients with hepatic impairment, consider the following dose reduction: (See Table 6)</td>
<td>(See Table 6)</td>
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<td>2.8 Dosage Modification with Concomitant Strong CYP3A4 Inhibitors</td>
<td>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.</td>
<td>(See Table 6)</td>
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<td>5 WARNINGS AND PRECAUTIONS 5.12 Hemorrhage</td>
<td>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, respectively. Grade 3 or 4 events 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.</td>
<td>(See Table 6)</td>
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<td>5.17 Fluid Retention</td>
<td>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.</td>
<td>(See Table 6)</td>
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</table>

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Last Updated: 12/2020

| NDA/ANDA/BLA Number, Label Version Date | Drug | Therapeutic Area | Biomarker† | Labeling Sections | Labeling Text
|---|---|---|---|---|---

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, 95th, 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
In Adult Patients with Newly Diagnosed Ph+ CML-CP
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. (...)

In Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
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
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) (...)

Laboratory Abnormalities
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) (...)

Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)
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 14/56 (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 treated with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP. (See Table 10) (...)

Additional Data from Clinical Trials
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:

1. Adult patients with newly diagnosed Ph+ CML-CP (n=60) 6-month analysis and
2. Adult patients with resistant or intolerant Ph+ CML-CP and CML-AP 24 months' analysis. (...)

In Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP
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 imatinib/dasatinib 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 90%.

In pediatric patients with Ph+ CML-CP, the most common (greater than or equal to 20%) non-hematologic adverse 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
In a multicenter, open-label, single-arm study of 58 pediatric patients with newly diagnosed or resistant Ph+ CML-CP 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 associated with growth retardation in 2 adolescent patients with body height below normal in the remaining pediatric patient (age category: child). Of the 58 pediatric patients, 12% (n = 7) experienced a decrease of two main height percentile lines compared with baseline (percentile lines: 5th, 10th, 25th, 50th, 75th, 95th, and 95th). Close monitoring of growth in pediatric patients under Tasigna treatment is recommended [see Warnings and Precautions (5.14)].

6 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
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).

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<td>Therapeutic</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. 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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<td>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 AUCO-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 AUCO-12h were 1540 ng/ml (48%) and 13337 ng h/ml (46%), respectively. (…)</td>
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<td>Specific Populations</td>
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<td>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.</td>
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<td>Pediatric Patients</td>
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<td>Following administration of the approved recommend 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 CML) and studies.</td>
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<td>Body surface area correlated with nilotinib clearance and was the primary factor responsible for the PK differences between pediatrics and adults.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Adult Newly Diagnosed Ph+ CML-CP</td>
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<td>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. (…)</td>
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<td>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) (…)</td>
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<td>14.2 Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP</td>
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<td>Study CAMN107A2101 (referred to as Study A2101) (NCT01010970) is an open-label, multicenter, 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 of treatment 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.</td>
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<td>14.3 Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)</td>
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<td>The ENESTop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Stop) study (NCT01698905) is an open-label, multicenter, single-arm study, where 153 adult patients with Ph+ CML-CP treated with Tasigna in first-line for ≥ 2 years who achieved MR4.5 as measured by 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:</td>
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<td>• The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year</td>
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<td>• The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS)</td>
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<td>• No more than two assessments falling between MR4 and MR4.5 (0.0032% IS &lt; BCR-ABL/ABL ≤ 0.01% IS).</td>
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<td>The median age of patients who entered the TFR phase was 55 years, 48.5% 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:</td>
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<td>• Loss of MMR requiring patient to reinitiate Tasigna treatment</td>
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<td>• When the BCR-ABL levels returned to a range between MR4.0 and MR4.5</td>
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<td>• When the BCR-ABL levels remained lower than MR4 for 4 consecutive measurements (8 weeks from initial loss of MR4.0)</td>
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<td>14.4 Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5) on Tasigna following prior imatinib therapy</td>
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<td>The ENESTop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Stop) 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 215 adult patients with Ph+ CML-CP treated with Tasigna in first-line for ≥ 2 years who achieved MR4.5 as measured by the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 adult 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:</td>
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<td>• The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year</td>
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<td>• The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS)</td>
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<td>• No more than two assessments falling between MR4 and MR4.5 (0.0032% IS &lt; BCR-ABL/ABL ≤ 0.01% IS).</td>
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<td>The median age of patients who entered the TFR phase was 55 years, 48.5% 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:</td>
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<td>• Loss of MMR requiring patient to reinitiate Tasigna treatment</td>
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<td>• When the BCR-ABL levels returned to a range between MR4.0 and MR4.5</td>
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<td>• When the BCR-ABL levels remained lower than MR4 for 4 consecutive measurements (8 weeks from initial loss of MR4.0)</td>
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</table>

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<td>022068, 09/25/2019</td>
<td>Nilotinib (2)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criterion: <em>The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during year 1. (…) Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL &gt; 0.01% IS were considered having a confirmed relapse of MR4.0, triggering restart of Tasigna treatment. Patients with loss of MMR in the TFR phase immediately restarted Tasigna treatment without confirmation. All patients who restarted Tasigna therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks. (…) 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 (NCT01775544), 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=25). In both studies, patients received Tasigna treatment at a dose of 230 mg/m² twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 450 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; BCR-ABL/ABL ≤ 0.1% IS) was 40.9% (18/44; 95% CI: 26.3%, 56.8%) at 12 cycles (28 days per cycle). In patients with newly diagnosed CML, the MMR rate was 60.0% (15/25; 95% CI: 38.7%, 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 11.3). For the 17 patients with newly diagnosed CML who achieved MMR, the median time to first MMR was 5.6 months (range: 2.7 to 16.6). Among patients with resistant or intolerant CML, 4.5% of patients achieved BCR-ABL/ABL ≤ 0.0032% IS (MR4.5) by the cut-off date. Among patients with newly diagnosed CML, the percentage of patients who achieved MR4.5 was 28.6%. (See Table 13) (…) 12.5 Pharmacogenomics Tasigna can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment. In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)7/TA7 genotypes. However, the largest increases in bilirubin were observed in the (TA)6/(TA)7 genotype (UGT1A1</em>28) patients [see Warnings and Precautions (5.6)]. 208447, 04/26/2020</td>
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<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>The trial demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the gBRCAmut cohort and the non-gBRCAmut cohort (Table 13, and Figures 3 and 4).</td>
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<td>125554, 01/22/2021</td>
<td>Nivolumab (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>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. (…) 14 CLINICAL STUDIES 14.1 Unresectable or Metastatic Melanoma Previously Treated Metastatic Melanoma (…) Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. (…) (…) Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%). (…) (…) There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. (…) Previously Untreated Metastatic Melanoma CHECKMATE-066 CHECKMATE-066 was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. (…) CHECKMATE-067 (…) Randomization was stratified by PD-L1 expression (≥5% vs. &lt;5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and N stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). (…) Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); 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 (…) Disease characteristics were AJCC Stage IIIb (34%), Stage IIIC (47%), Stage IV (19%), M1b-a (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (9%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%). (…)</td>
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<td>125554, 01/22/2021</td>
<td>Nivolumab (2)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration</td>
<td>1 INDICATIONS AND USAGE 1.3 Metastatic Non-Small Cell Lung Cancer</td>
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<td>Administration, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
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</tbody>
</table>

**2 DOSE AND ADMINISTRATION**

**2.1 Patient Selection**

Select patients with metastatic NSCLC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression [see Clinical Studies (14.3)]. Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

**2.2 Recommended Dosage**

The recommended dosages of OPDIVO as a single agent are presented in Table 1. (See Table 2)

### 8 USE IN SPECIFIC POPULATIONS

**8.5 Geriatric Use**

Of the 576 patients randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received OPDIVO with ipilimumab (18%). Of the 596 patients in the primary efficacy population (PD-L1 ≥1%) randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older [see Clinical Studies (14.3)].

**12 PHARMACOKINETICS**

**Specific Populations**

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR ≥ 15 mL/min/1.73 m²), and tumor ulceration (32%). (…)

**14 CLINICAL STUDIES**

#### 14.3 Pharmacokinetics

**Specific Populations**

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, 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). (…)

**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 vs. M1c). (…)

**CHECKMATE-067**

(…) Randomization was stratified by PD-L1 expression (25% 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). (…) 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%). (…) Disease characteristics were: median age 61 years (range: 18 to 90); 96% male; 97% White; ECOG performance score (0–3); or 71% (3%) or 27% (12%) Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); 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%). (…) 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%). (…)

**14.2 Adjuvant Treatment of Melanoma**

**CHECKMATE-238**

(…) Randomization was stratified by PD-L1 status (positive [based on 5% level] vs. negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage III/III vs. Stage IV M0/M1a/M1b vs Stage IV M1c). (…) Disease characteristics were AJCC Stage III (34%), Stage IV (19%), M1a-b (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 (15 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. (…) Disease characteristics were: median age 64 years (range: 26 to 87); 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 ≥1%, 29% with squamous and 71% with nonsquamous histology, 10% had brain metastases, and 85% were former/current smokers. (…) Disease characteristics were: median age 64 years (range: 26 to 87); 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 ≥1%, 29% with squamous and 71% with nonsquamous histology, 10% had brain metastases, and 85% were former/current smokers. (…) Disease characteristics were: median age 64 years (range: 26 to 87); 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 ≥1%, 29% with squamous and 71% with nonsquamous histology, 10% had brain metastases, and 85% were former/current smokers. (…)

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First-line Treatment of Metastatic or Recurrent NSCLC In Combination with Ipilimumab and Platinum-Doubled Chemotherapy
CHECKMATE-6LA (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 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% vs. 1%-<5% vs. ≥5%). The median age was 65 years (range; 26 to 98) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were white (69%) 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 <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. (...) Second-line Treatment of Metastatic Squamous NSCLC
CHECKMATE-017
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 level. (...) Archival tumor specimens were retrospectively evaluated for PD-L1 expression in the PD-L1 negative subgroup and 0.95 (CI: 0.45, 1.05) in the PD-L1 positive NSCLC subgroup. (...) Second-line Treatment of Metastatic Non-Squamous NSCLC
CHECKMATE-057
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 level. (...) Archival tumor specimens were retrospectively 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% (209/455) 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. (...) 14.4 Small Cell Lung Cancer
CHECKMATE-032 (NCT01993934) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic solid tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinum-based chemotherapy to receive treatment with OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. (...) 14.5 Advanced Renal Cell Carcinoma
Previously Treated Renal Cell Carcinoma
CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after or two or more 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) (...) Previously Untreated Renal Cell Carcinoma
CHECKMATE-214 (NCT02317499) 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) (...) Studies evaluated the efficacy of OPDIVO as a single agent in adult patients with aHL after failure of autologous HSCT.
CHECKMATE-9ER
CHECKMATE-9ER was a randomized, open-label study of OPDIVO combined with cabozantinib versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression (>1% vs. 1%-<5% vs. ≤1%), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World). (...) The major efficacy outcome measure was PFS (BCR Assessed). Additional efficacy outcome measures were OS and ORR (BCR Assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to OPDIVO and cabozantinib compared with sunitinib. (*) Therapeutic areas do not necessarily reflect the CDER review division.
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<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>1 INDICATIONS AND USAGE</td>
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**1.9 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer**

OPDIVO, 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.

**2 DOSAGE AND ADMINISTRATION**
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<td>1.3 Metastatic Non-Small Cell Lung Cancer</td>
<td>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.</td>
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<tr>
<td><strong>6 ADVERSE REACTIONS</strong></td>
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<tr>
<td>14.3 Metastatic Non-Small Cell Lung Cancer</td>
<td>OPDIVO, in combination with ipilimumab and 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.</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.
## Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2020**

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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<th>Biomarker‡</th>
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<td>Nusinersen</td>
<td>Neurology</td>
<td>SMN2</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td><em>Therapeutic areas do not necessarily reflect the CDER review division.† 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.</em></td>
</tr>
</tbody>
</table>

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 (NCT01673887) 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-doubled-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 (62%) 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%); 78% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. (…)"
<table>
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<th>Biomarker</th>
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<td>Obinutuzumab</td>
<td>Oncology</td>
<td>MS4A1 (CD20 antigen)</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Infantile-Onset SMA</td>
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<td>(...) Baseline demographics were balanced between the SPINRAZA and control groups with the exception of age at first treatment (median age 175 vs. 206 days, respectively). The SPINRAZA and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number. (...)</td>
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<td>14.3 Presymptomatic SMA</td>
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<td>(...) Some patients receiving SPINRAZA before the onset of SMA symptoms survived without requiring permanent ventilation beyond what would be expected based on their SMN2 copy number, and some patients also achieved age-appropriate growth and developmental motor milestones such as the ability to sit unassisted, stand, or walk.</td>
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<tr>
<td>208558, 12/07/2020</td>
<td>Olaparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
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<td></td>
<td></td>
<td>1.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer</td>
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<td>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)).</td>
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<td>1.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab</td>
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<td>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)).</td>
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<td>1.4 Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy</td>
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<td>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)).</td>
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<td>1.5 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer</td>
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<td>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)).</td>
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<td>1.6 First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma</td>
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<td>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)).</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td></td>
<td>2.1 Patient Selection</td>
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<td>Information on FDA-approved tests for the detection of genetic mutations is available at <a href="http://www.fda.gov/companiondiagnostics">http://www.fda.gov/companiondiagnostics</a>. 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).</td>
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<td>2.2 Recommended Dosing</td>
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<td>First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer</td>
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<td>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.</td>
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<td>Recurrent Ovarian Cancer, Germline BRCAm Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer</td>
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<td>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. (...)</td>
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#### 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% (23/2351) and the majority of events had a fatal outcome. Of these, 2528 patients had a documented BRCA mutation, 2 patients had gBRCA wildtype and in 1 patient the BRCA mutation status was unknown. (…)

#### 6 ADVERSE REACTIONS

**First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer**

SOLO-1

The safety of Lynparza for the maintenance treatment of patients with BRCA-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1, a placebo-controlled, double-blind study in which 390 patients received either Lynparza 300 mg BID (n=260) or placebo tablets (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo. (…)

**Maintenance Treatment of Recurrent Ovarian Cancer**

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive gBRCAm ovarian cancer was investigated in SOLO-2. This study was a placebo-controlled, double-blind study in which 294 patients received either Lynparza 300 mg (2 x 150 mg tablets) twice daily (n=195) or placebo tablets twice daily (n=99) until disease progression or unacceptable toxicity. (…)

**Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy**

Pooled data

The safety of Lynparza was investigated in 223 patients (pooled from 6 studies) with gBRCAm advanced ovarian cancer who had received 3 or more prior lines of chemotherapy [see Clinical Studies (14.4)]. Patients received Lynparza capsules 400 mg orally twice daily until disease progression or unacceptable tolerability. The median exposure to Lynparza in these patients was 5.2 months. (…)

**Germline BRCA-mutated HER2-negative Metastatic Breast Cancer**

OlympiAD

The safety of Lynparza was evaluated in gBRCAm patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD [see Clinical Studies (14.5)]. (…)

**First-line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma**

POLO

The safety of Lynparza as maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma following first-line treatment with platinum-based chemotherapy was evaluated in POLO [see Clinical Studies (14.6)]. (…)

#### 14 CLINICAL STUDIES

**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, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy. (…)

A total of 361 patients were randomized, 260 to Lynparza and 131 to placebo. The median age of patients treated with Lynparza was 53 years (range: 29 to 82) and 53 years (range: 31 to 84) among patients on placebo. The ECOG performance status (PS) was 0 in 77% of patients receiving Lynparza and 80% of patients receiving placebo. Of all patients, 82% were White, 36% were enrolled in the U.S. or Canada, and 82% were in complete response to their most recent platinum-based regimen. The majority of patients (n=339) had germline BRCA mutation (gBRCAm), and 2 patients had somatic BRCAm (sBRCAm). Of the 391 patients randomized in SOLO-1, 368 were retrospectively or prospectively tested with a Myriad BRACAnalysis test and 383 patients were confirmed to have deleterious or suspected deleterious gBRCAm status; 253 were randomized to the Lynparza arm and 130 to the placebo arm. Two of 391 patients randomized in SOLO-1 were confirmed to have sBRCAm based on an investigational Foundation Medicine tissue test. (…)

**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 (timings and outcomes of cytoreductive surgery and response to platinum-based chemotherapy) and IBCam 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.

**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=286). (…)

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1.5 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. (…)

1.6 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=106), 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.

14.4 Advanced Germline BRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy

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 gBRCAm mutation, including 39% (n=53) of patients on placebo. (…) The median age of the patients was 58 years, the majority were White (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious gBRCAm status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the BRACAnalysis CDx®. (See Table 22). (…)

14.5 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. (…)

14.6 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=106), 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. 14.7 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, Bripp1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPF2R2A, 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 F1CDx 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) Consistent results were observed in exploratory analyses of rPFS for patients who received or did not receive prior taxane therapy and for those with germline-BRCA mutations identified using the Myriad BRACAnalysis CDx® assay compared with those with BRCA mutations identified using the Foundation Medicine F1CDx assay. (See Table 27).

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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>
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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. (…) 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 [link].

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

Recurrent Ovarian Cancer, Germline BRCA-mutated Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRD Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- Maintenance treatment of recurrent ovarian cancer

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| 208558, 12/07/2020                      | 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  
Olaparib 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)]. |

| 208558, 12/07/2020                      | 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)]. |

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</table>
| 208558, 12/07/2020                     | Olaparib (5) | Oncology | Homologous Recombination Repair | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years. When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for bevacizumab when used in combination with Lynparza for more information. Recurrent Ovarian Cancer, Germline BRCAm 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 orchiectomy. 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 IBCaM 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=255) 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)]. 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. 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 BRCAm 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 orchiectomy. 6 ADVERSE REACTIONS 6.1 Clinical Trial Experience

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<th>Labeling Text‡</th>
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<td>208558, 12/07/2020</td>
<td>Olaparib (6)</td>
<td>Oncology</td>
<td>PPP2R2A</td>
<td>Clinical Studies</td>
<td>HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer</td>
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<td>Olaratumab</td>
<td>Oncology</td>
<td>PDGFRA</td>
<td>Clinical Studies</td>
<td>HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer</td>
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<td>210730, 08/07/2020</td>
<td>Oliceridine</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>Omeprazole</td>
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<td>207931, 07/23/2018</td>
<td>Ombitasvir, Paritaprevir, and Ritonavir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
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<tr>
<td>022056, 08/21/2018</td>
<td>Ondansetron</td>
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<td>Gastroenterology</td>
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require less frequent dosing. These patients should be closely monitored for respiratory depression and sedation at frequent intervals, and subsequent doses should be based on the patient's severity of pain and response to treatment. (…)

8 USE IN SPECIFIC POPULATIONS
8.5 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. [See Warnings and Precautions (5.6), Clinical Pharmacology (12.5)].

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Drug Interaction Studies
In vitro studies suggest that olliceridine 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 olliceridine in these assays, suggesting that the contribution of CYP2C9 and CYP2C19 to the metabolism of olliceridine 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 olliceridine 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 iraconazole 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 olliceridine was reduced to approximately 30% of that observed in nonpoor metabolizers of CYP2D6 [see Drug Interactions (7)].

12.5 Pharmacogenomics
Olliceridine 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 AUC0-inf of olliceridine was approximately 2-fold higher than in subjects who are nonpoor CYP2D6 metabolizers. See Warnings and Precautions (5.6), Use in Specific Populations (8.8).

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<tbody>
<tr>
<td>208065, 12/18/2020</td>
<td>Osimertinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>1 INDICATIONS AND USAGE</td>
<td>1.1 Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) TAGRISSO is indicated as adjuvant therapy after tumor resection in adult 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)]. 1.2 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)]. 1.3 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)].</td>
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</table>
| 203505, 01/25/2019                      | 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 S-warfarin with and without ospemifene for Cmax and AUC0-inf were 0.97 (0.92-1.02) and 0.96 (0.91-1.02), 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, 01/25/2019                      | 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 after overnight fast, a single 150 mg sustained release bupropion was administered in morning under fasted condition. The geometric mean ratio (80% CI) for bupropion with and without ospemifene for Cmax and AUC0-inf were 0.97 (0.75-0.91) and 0.81 (0.77-0.86), respectively. The geometric mean ratio (80% 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 Oxtellar 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 Oxtellar 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 SJS/TEN with Oxtellar XR. The frequency of HLAB*1502 allele ranges from 2 to 12% in Han Chinese populations, is about 8% in Thai populations, and above 1% in other Asian populations. |

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<td>Oxytetracaine and Tetracaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
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<td>5.1 Methemoglobinemia</td>
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<td>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>
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<tr>
<td>208032, 11/02/2018</td>
<td>Oxytetracaine and Tetracaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions</td>
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<td>207103, 09/09/2019</td>
<td>Palbociclib (1)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>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.</td>
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<td>6.1 Clinical Studies Experience</td>
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<td>Study 1: IBRANCE plus Letrozole</td>
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<td>Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy</td>
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<td>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 669 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. (…)</td>
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<td>Study 2: IBRANCE plus Fulvestrant</td>
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<td>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</td>
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<td>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. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>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. (…)</td>
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| 207103, 09/09/2019                      | Palbociclib (2) | Oncology       | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 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. (…)

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;
- 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 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 444 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 12.3 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 12.3 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 antagonist 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, clinicopharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.
| 125147, 06/29/2017 | Panitumumab (1) | Oncology | EGFR | Adverse Reactions, Clinical Pharmacology, Clinical Studies 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (…) Safety data are presented from two clinical trials in which patients received Vectibix: Study 200320408, an open-label, multinational, randomized, controlled, single-arm study in patients with EGFR-expressing mCRC and Study

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<th>Labeling Text&lt;sup&gt;‡&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>125147, 06/29/2017</td>
<td>Panitumumab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>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 658 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.</td>
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</table>

**1 INDICATIONS AND USAGE**

**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 fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy [see Clinical Studies (14.1)].

**12 CLINICAL PHARMACOLOGY**

**12.3 Pharmacokinetics**

(….) A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age (21-88 years), gender, race (15% nonwhite), mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, and 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab. No formal pharmacokinetic studies of panitumumab have been conducted in patients with renal or hepatic impairment.

**14 CLINICAL STUDIES**

**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 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum, in Study 2008763, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type KRAS mCRC, and in Study 2010007, an open-label, multicenter, multinational, randomized trial of 377 patients with wild-type KRAS mCRC. (…) 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 658 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. (…) Vectibix in Combination with FOLFOX Chemotherapy

The most commonly reported adverse reactions (≥ 2% difference between treatment arms) in Vectibix-treated patients with

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wildtype KRAS mCRC were diarrhea and dehydration. The commonly reported adverse reactions (≥ 1%) leading to discontinuation in patients with wild-type KRAS mCRC receiving Vectibix were rash, paresthesia, fatigue, diarrhea, acneform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypokalemia, occurred in a patient who received Vectibix. (See Table 2) (…)

14 CLINICAL STUDIES

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 463 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 (NCT01001377) 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 or 1 vs 2) in patients with wild-type KRAS mCRC. (See Table 3 and Figure 1) (…) Study 20100007 (NCT01412487)

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 irinotecan, 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. The primary efficacy outcome measure was OS in patients with wild-type KRAS mCRC. Secondary efficacy outcomes included OS in the subgroup of patients with wild-type RAS mCRC. (…) KRAS tumour mutation status was available for all patients and RAS tumour 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 56% of patients, 1 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) (…) (See Figure 3) Exploratory Analysis of OS

An exploratory analysis of OS with updated information based on events in 82% of patients with wild-type KRAS mCRC estimated the treatment effect of Vectibix plus FOLFOX compared with FOLFOX alone on OS (Figure 3). Median OS among 325 patients who received Vectibix plus FOLFOX was 23.8 months (95% CI: 20.0, 27.7) vs 19.4 months (95% CI: 17.4, 22.6) among 331 patients who received FOLFOX alone (HR = 0.83, 95% CI: 0.70, 0.98). (See Figure 3) Retrospective exploratory analyses in the RAS wild-type subgroup Among the 656 patients with wild-type KRAS exon 2 mCRC, RAS mutation status was assessed for 620 patients using Sanger bidirectional sequencing and Surveyor®/WAVE® analysis. Of these 620 patients, approximately 17% of patients (n = 104) tumors harbored mutations in KRAS exons 3 or 4 or in NRAS exons 2, 3, and 4. Retrospective subset analyses were then conducted among the subset of patients without RAS mutations (n = 512) as described above.

In the wild-type RAS subgroup, 65% of patients were men and 91% were White, 2% Black, and 5% Hispanic or Latino. Sixty-five percent of patients had colon cancer and 35% had rectal cancer. ECOG performance was 0 in 57% of patients, 1 in 37% of patients, and 2 in 6% of patients. Median age was 61 years. (See Table 6 and Figure 4)

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 272 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 (95% CI: 13.4, 17.9) among patients receiving Vectibix plus FOLFOX and 19.2 months (95% CI: 16.7, 21.8) among patients who received FOLFOX alone (HR = 1.25, 95% CI: 1.02, 1.55).

In Study 20100007, among patients with RAS-mutant tumors, no differences in OS or PFS were observed between the treatment arms (n = 54; OS HR = 0.99 (95% CI: 0.49, 2.00); PFS HR = 1.03 (95% CI: 0.56, 1.98).

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| 020987, 04/25/2019                     | Pantoprazole       | Gastroenterology| CYP2C19    | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
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.  
12.5 Pharmacogenomics  
CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10 hours in adults, they still have minimal accumulation (23% or less) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed. Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10 fold lower apparent oral clearance compared to extensive metabolizers. For known pediatric poor metabolizers, a dose reduction should be considered. |
| 125511, 12/17/2018                     | Parathyroid Hormone | Inborn Errors of Metabolism | CASR | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE  
NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.  
Limitations of Use:  
• 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)).  
• NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.  
• NATPARA was not studied in patients with acute post-surgical hypoparathyroidism. |
| 020031, 01/04/2017                     | Paroxetine         | Psychiatry      | CYP2D6     | Drug Interactions, Clinical Pharmacology | DRUG INTERACTIONS  
Drugs Metabolized by CYP2D6:  
(…) 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.  
CLINICAL PHARMACOLOGY  
Pharmacokinetics: Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets of PAXIL daily for 30 days. Paroxetine is extensively metabolized and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers). |
| 219922, 08/10/2018                     | Patinsiran         | Neurology       | TTR        | Adverse Reactions, Clinical Pharmacology, Clinical Studies | 6 ADVERSE REACTIONS  
(…) 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 transthyretin 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.  
12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
(…) Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race.  
14 CLINICAL STUDIES  
(…) Patients receiving ONPATTRO experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, Val30Met mutation status, and disease stage. |
| 022465, 06/02/2020                     | Pazopanib (1)      | Oncology        | UGT1A1     | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.5 Pharmacogenomics  
Pazopanib can increase serum total bilirubin levels (see Warnings and Precautions (5.1)). In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. A pooled pharmacogenetic analysis of 236 Caucasian patients evaluated the TA-repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during pazopanib treatment. In this analysis, the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic |
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<tr>
<td>024265, 06/02/2020</td>
<td>Pazopanib (2)</td>
<td>Oncology</td>
<td>HLA-B</td>
<td>Clinical Pharmacology</td>
<td>susceptibility to Gilbert’s syndrome was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes.</td>
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<td>103849, 01/08/2019</td>
<td>Peginterferon Alfa-2b</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics In a pooled pharmacogenetic analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, ALT &gt; 2x ULN (NCI CTC Grade 2) occurred in 32% (42/133) of HLA-B<em>57:01 allele carriers and in 19% (36/191) of non-carriers and ALT &gt; 5x ULN (NCI CTC Grade 3) occurred in 19% (25/133) of HLA-B</em>57:01 allele carriers and in 10% (213/2101) of non-carriers. In this dataset, 6% (133/2234) of the patients carried the HLA-B*57:01 allele. Liver function should not be monitored in all subjects receiving pazopanib, regardless of genotype [see Warnings and Precautions (5.1)].</td>
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<td>125263, 07/13/2018</td>
<td>Pegloticase</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Clinical Pharmacology</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>
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<tr>
<td>125514, 11/13/2020</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 Ipilimumab-Refractory Melanoma The safety of KEYTRUDA in patients with unsectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. (…) 14 CLINICAL STUDIES 14.1 Melanoma (ipilimumab-Naive Melanoma) (…) Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. (…) (…) 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, 60% White, 60% had no prior systemic therapy for metastatic disease, 60% 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 i2o 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, 19% (46%) 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 [≥1.10 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 or two 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. (…)</td>
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<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>(…) 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. (…)</td>
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## Melanoma

### Ipilimumab-Refractory Melanoma

(…) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥1.10 UNL]) 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. The trial excluded patients with uveal melanoma and active brain metastasis. (…) The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator’s choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance status 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V6000 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. (…) **Adjuvant Treatment of Resected Melanoma** (…) 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 IIIA, 46% had stage IIIB, 18% had stage IIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥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 IHC assay. (…) **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.

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<td>CD274 (PD-L1)</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.2 Non-Small Cell Lung Cancer</td>
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<td>KEYTRUDA, in combination with pembrolizumab and platinum-based 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.</td>
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<td>KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.</td>
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<td>KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 (Tumor Proportion Score (TPS) ≥1%) as determined by an FDA-approved test (see Dosage and Administration (2.1)), with no EGFR or ALK genomic tumor aberrations, and is:</td>
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<td>• stage III where patients are not candidates for surgical resection or definitive chemoradiation, or</td>
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<td>• metastatic.</td>
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<td>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.</td>
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<td>1.4 Head and Neck Squamous Cell Cancer</td>
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<td>KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).</td>
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<td>KEYTRUDA, as a single agent, is indicated for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC 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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<td>KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.</td>
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<td>1.7 Urothelial Carcinoma</td>
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<td>KEYTRUDA 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 (CPS ≥10) as determined by an FDA-approved test (see Dosage and Administration (2.1)), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response (see Clinical Studies (14.7)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
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<td>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.</td>
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<td>1.9 Gastric Cancer</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal juncture adenocarcinoma whose tumors express PD-L1 (Combined Positive Score (CPS) ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidines and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy (see Clinical Studies (14.7)). This indication is approved under accelerated approval based on tumor response rate and durability of response. 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>1.10 Esophageal Cancer</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test (see Dosage and Administration (2.1)), with disease progression after one or more prior lines of systemic therapy.</td>
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<td>1.11 Cervical Cancer</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy 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 (14.10)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.</td>
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1.19 Triple-Negative Breast Cancer

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test [see Dosage and Administration (2.1)].

This indication is approved under accelerated approval based on progression-free survival [see Clinical Studies (14.19)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSEAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H Cancer, or TMB-H Cancer

(…) 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 (14.16)].

For the MSI-H/dMMR indication, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens [see Clinical Studies (14.8)].

Because the effect of prior chemotherapy on test results for tumor mutation burden (TMB-H), MSI-H, or dMMR in patients with high-grade gliomas is unclear, it is recommended to test for these markers in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Information on FDA-approved tests for the detection of PD-L1 expression and TMB status is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of MSI-H or dMMR is not currently available. (See Table 2)

6 ADVERSE REACTIONS

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)]. (…)

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 cHL, 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 (14.5, 14.6, 14.8, 14.14, 14.17)].

In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive solid tumors received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults included pyrexia (30%), vomiting (30%), upper respiratory tract infection (20%), and headache (25%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (30%), neutropenia (26%), and Grade 3 anemia (17%).

The safety and effectiveness of KEYTRUDA in pediatric patients have not been established in the other approved indications [see Indications and Usage (1)].

14 CLINICAL STUDIES

14.1 Melanoma

Biomab: Naive Melanoma

(…) Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. (…)

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 66% had no prior systemic therapy for metastatic disease; 69% ECOG PS 0; 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay; 65% had M1c stage disease; 69% with normal LDH; 36% with reported BRAF mutationpositive melanoma; and 6% with a history of brain metastases. Among patients with BRAF mutationpositive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. (…)

Adjuvant Treatment of Resected Melanoma

(…) 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 IIIA, 46% had stage IIIB, 18% had stage IIE (1-3 positive lymph nodes), and 20% had stage IIE (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 IUO 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 pemetrexed and platinum chemotherapy

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|                                        |                       |           |                   | 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 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 (captoplan 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 score of 1; and 18% 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 either paclitaxel or nab-paclitaxel chemotherapy.
|                                        |                       |           |                   | The efficacy of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407 (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%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). (…)
|                                        |                       |           |                   | 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 PS of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% (negative). Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/PD-L1 monoclonal antibody at the time of disease progression. (See Table 35) (…)
|                                        |                       |           |                   | First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy.
|                                        |                       |           |                   | The efficacy of KEYTRUDA in combination with carboplatin and investigator’s choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407 (NCT02775435), a randomized, multicenter, 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%), choice of paclitaxel or paclitaxel protein-bound, and geographic region (East Asia vs. non-East Asia). (…)
|                                        |                       |           |                   | The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; 71% ECOG PS of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS <1%; 19% were from the East Asian region; and 60% received paclitaxel.
|                                        |                       |           |                   | First-line treatment of metastatic NSCLC as a single agent.
|                                        |                       |           |                   | KEYNOTE-042
|                                        |                       |           |                   | 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 with tumor PD-L1 expression (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 thoracic radiation within the prior 26 weeks 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 to chemotherapy. Table 37 and Figure 8 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 ≥1% and those with PD-L1 TPS ≤50%. 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
|                                        |                       |           |                   | The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (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 and who had not received prior systemic therapy for metastatic NSCLC were eligible. (…)
|                                        |                       |           |                   | 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 score of 1; and 18% with history of brain metastases. (See Table 35) (…)
|                                        |                       |           |                   | 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 score of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS ≥1% (negative). Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/PD-L1 monoclonal antibody at the time of disease progression. (See Table 35) (…)

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<td><strong>14.4 Head and Neck Squamous Cell Cancer</strong></td>
<td>First-line treatment of metastatic or unresectable, recurrent HNSCC.</td>
<td>The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 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 &lt;50%) according to the PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (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 ≥2. (...) 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 in combination 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 ≥2 (HR 0.69, 95% CI:0.51, 0.94).</td>
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<td><strong>14.7 Urothelial Carcinoma</strong></td>
<td>Cisplatin ineligible Patients with Urothelial Carcinoma</td>
<td>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) (...) 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 &lt;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.</td>
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<td><strong>14.8 Microsatellite Instability-High Cancer</strong></td>
<td>(See Table 48)</td>
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<td><strong>14.9 Gastric Cancer</strong></td>
<td>(See Table 49)</td>
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<td><strong>14.10 Esophageal Cancer</strong></td>
<td>KEYNOTE-181</td>
<td>The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02654263), 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. (...) 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.</td>
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<td><strong>KEYNOTE-180</strong></td>
<td>Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The baseline characteristics of these 35 patients were: median age of 65 years (range: 47 to 81), 51% age 65 or older; 71% male; 26% White and 69% Asian; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. One hundred percent had M1 disease. The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8, 37). Among the 73 responding patients, the DoR ranged from 4.2 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer.</td>
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<td><strong>14.11 Cervical Cancer</strong></td>
<td>Among the 98 patients in Cohort E, 77% (n=45) had tumors that expressed PD-L1 with a CPS ≥1 and received at least one line of chemotherapy in the metastatic setting; PD-L1 status was determined using the IHC 22C3 pharmDx kit. The baseline characteristics of these 77 patients were: median age of 45 years (range: 27 to 76); 81% White; 14% Asian, and 3% Black; 32% ECOG PS of 0 and 68% ECOG PS of 1; 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology; 95% had M1 disease and 5% had recurrent disease; and 35% had one and 65% had two or more prior lines of therapy in the recurrent or metastatic setting.</td>
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<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>No responses were observed in patients whose tumors did not have PD-L1 expression (CPS &lt;1). Efficacy results are summarized in Table 53 for patients with PD-L1 expression (CPS ≥1). (...) 14.14 Renal Cell Carcinoma The efficacy of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 (NCT02853331) in a randomized, multicenter, open-label trial conducted in 681 patients who had received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease requiring systemic immunosuppression within the last 2 years were ineligible. (...) Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status. (...) 14.19 Triple-Negative Breast Cancer The efficacy of KEYTRUDA in combination with paclitaxel, paclitaxel-protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial conducted in 847 patients with locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, who had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by chemotherapy treatment (paclitaxel or paclitaxel-protein-bound vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS ≥1 vs. CPS &lt;1) according to the PD-L1 IHC 22C3 pharmDx kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no). (...) The study population characteristics for patients were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of patients had tumor PD-L1 expression CPS ≥1 and 38% had tumor PD-L1 expression CPS ≥0. Table 58 and Figure 16 summarize the efficacy results for KEYNOTE-355.</td>
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</table>

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# Table of Pharmacogenomic Biomarkers in Drug Labeling

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| NDA/ANDA/BLA Number, Label Version Date | Drug | Therapeutic Area* | Biomarker† | Labeling Text
---|---|---|---|---
| 125514, 11/13/2020 | Pembrolizumab (4) | Oncology | EGFR | The safety of KEYTRUDA in combination with lenvatinib (20 mg orally once daily) was investigated in KEYNOTE-146, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumors had progressed following one line of systemic therapy and were not MSI-H or dMMR [see Clinical Studies (14.10)]. (…) 8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use The safety and effectiveness of KEYTRUDA have been established in pediatric patients with cHL, PMBCL, and MSI-H cancer. Use of KEYTRUDA in pediatric patients with cHL, PMBCL, and MSI-H cancers is supported by evidence from adequate and well-controlled studies of KEYTRUDA in adults with additional pharmacokinetic and safety data in pediatric patients [see Adverse Reactions (6.1), Clinical Studies (14.4, 14.5, 14.7), Clinical Pharmacology (12.3), Clinical Studies (14.5, 14.6, 14.8, 14.14, 14.17)]. 14 CLINICAL STUDIES 14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer The efficacy of KEYTRUDA was investigated in patients with MSI-H or dMMR cancers. 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; 64% White, 18% Asian, and 2% Black; and 54% ECOG PS of 0 and 56% ECOG 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 had 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) 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 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 24 were identified using both tests. Efficacy results are summarized in Tables 66 and 57. 14.9 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 207 patients with previously untreated metastatic or advanced MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded. (See Table 58) (…) 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 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 three prior lines of therapy in the recurrent or metastatic setting. (…) Among the 259 patients enrolled in KEYNOTE-059, 7 (3%) had tumors that were determined to be MSI-H. An objective response was observed in 4 patients, including 1 complete response. The DoR ranged from 5.3+ to 14.14 months. 14.16 Endometrial Carcinoma Among the 108 patients, 87% (n=94) had tumors that were not MSI-H or dMMR. 10% (n=11) had tumors that were MSI-H or dMMR, and in 3% (n=3) the status was not known. Tumor MSI status was determined using a polymerase chain reaction (PCR) test. Tumor MMR status was determined using an IHC test. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years, 62% age 65 or older; 62% White, 6% Black, 4% Asian, and 3% other races; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior systemic therapy for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies. 1 INDICATIONS AND USAGE 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. KE... 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience NSCLC

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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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<td>1.2 Non-Small Cell Lung Cancer</td>
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<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. (…)</td>
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<td>KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic squamous NSCLC. (…)</td>
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<td>KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test (see Dosage and Administration (2.1)), with no EGFR or ALK genomic tumor aberrations, and is: (…)</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience NSCLC</td>
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<tr>
<td>First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy. (…)</td>
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| 125514, 11/13/2020 | Pembrolizumab | Oncology | Tumor Mutational Burden | Indications and Usage, Dosage and Administration, Clinical Studies | 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=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 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. (…)
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 not 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 as a single agent
KEYNOTE-042
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. (…)
Previously 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. (…)
(…) 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. All patients had received prior therapy with a platinum-containing regimen. 29% received two or more prior therapies for their metastatic disease. (…)

1 TUMOR MUTATIONAL BURDEN-HIGH CANCER
1.16 Tumor Mutational Burden-High Cancer
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 confirmatory trials. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H Cancer, or TMB-H Cancer
(…) 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 (14.16)]. For the MSI-H/dMMR indication, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR tumor status in tumor specimens [see Clinical Studies (14.18)].
Because the effect of prior chemotherapy on test results for tumor mutation burden (TMB-H), MSI-H, or dMMR in patients with high-grade gliomas is unclear, it is recommended to test for these markers in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas. Information on FDA-approved tests for the detection of PD-L1 expression and TMB status is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of MSI-H or dMMR is not currently available. (See Table 2)

14 CLINICAL STUDIES
14.16 Tumor Mutational Burden-High Cancer
The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with high tumor mutation burden (TMB-H) who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). (…)

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<tbody>
<tr>
<td>213736, 04/17/2020</td>
<td>Pemigatinib</td>
<td>Oncology</td>
<td>FGFR2</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>PEMAZYRE is indicated for the treatment of adults with previously treated, unrespectable 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).</td>
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<td>010775, 05/10/2002</td>
<td>Perphenazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions, Clinical Pharmacology</td>
<td>Drug Interactions of a number of medications, including antipsychotics, antidepressants, β-blockers, and antihistamines, occurs through the cytochrome P450 2D6 (CYP 2D6) metabolic pathway. Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called &quot;poor&quot; 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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</table>
| 125409, 01/16/2020                     | Pertuzumab (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical | 1 INDICATIONS AND USAGE: 

1.1 Metastatic Breast Cancer (MBC) PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. 

1.2 Early Breast Cancer (EBC) PERJETA is indicated for use in combination with trastuzumab and chemotherapy for • the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer [see Dosage and Administration (2.2) and Clinical Studies (14.2)]. |

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<td>Pharmacology, Clinical Studies</td>
<td>• the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence [see Dosage and Administration (2.2) and Clinical Studies (14.3)].</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>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 cancer 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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>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.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Left Ventricular Dysfunction</td>
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<td>Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered [Dosage and Administration (2.3)]. (…)</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>Adjuvant Treatment of Breast Cancer (APHINITY)</td>
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<td>The adverse reactions described in Table 6 were identified in 4769 patients with HER2-positive early breast cancer treated in APHINITY. (…)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.6 Cardiac Electrophysiology</td>
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<td>The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in CLEOPATRA. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Metastatic Breast Cancer</td>
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<td>CLEOPATRA (NCT00567196) was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer treated in Study 1. (…)</td>
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<td>14.2 Neoadjuvant Treatment of Breast Cancer</td>
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<td>NeoSphere (NCT00546688) was a multicenter, randomized trial conducted in 471 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment. (…)</td>
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<td>Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab. (…)</td>
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<td>14.3 Adjuvant Treatment of Breast Cancer</td>
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<td>APHINITY (NCT01358877) was a multicenter, randomized, double-blind, placebo-controlled study conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. (…)</td>
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<tr>
<td>Pertuzumab</td>
<td>Oncology</td>
<td>ESR, PGR</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<tr>
<td>125409,</td>
<td></td>
<td>(Hormone Receptor)</td>
<td></td>
<td>14.1 Metastatic Breast Cancer</td>
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<tr>
<td>01/16/2020</td>
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<td>(…) Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 49%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.96). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52). (…)</td>
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<td>14.2 Neoadjuvant Treatment of Breast Cancer</td>
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<tr>
<td>NeoSphere</td>
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<td>(…) Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. (…)</td>
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<td>(…) Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR positive). (…)</td>
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<td>(…) The PCR rates and magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors. (See Table 8) (…)</td>
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<td>14.3 Adjuvant Treatment of Breast Cancer</td>
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<tr>
<td>TRYPHAENA</td>
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<td>(…) The PCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI: 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with hormone receptor-negative tumors: 73.5% (95% CI: 56.5%, 87.1%), 62.5% (95% CI: 45.8%, 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively. (…)</td>
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<td>14.4 Treatment of Breast Cancer</td>
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<tr>
<td>NeoSphere</td>
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<td>(…) Demographics were generally balanced between the two treatment arms. The median age was 51 years (range 18-80). 13% of patients were 65 or older, and over 99% of patients were female. Sixty-three percent of patients had node-positive disease, 64% had hormone receptor-positive disease, and 71% were Caucasian. All patients had an ECOG performance status of 0 or 1. Seventy-eight percent received an anthracycline containing regimen. (See Tables 9 and 10) (…)</td>
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<tr>
<td>NeoSphere</td>
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<td>(…) The pCR (ypT0/is ypN0) rates were 61.8% (95% CI: 54.7, 68.6) and 60.7% (95% CI: 53.6, 67.5) for patients treated with dAC followed by PERJETA plus trastuzumab and docetaxel, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 51.6% (95% CI: 42.6, 60.5%) and 57.3% (95% CI: 48.1, 66.1%) than with hormone receptor-negative tumors: 81.5% (95% CI: 70.0, 90.1%) and 68.0% (95% CI: 56.2, 79.3%) respectively. (…)</td>
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<td>NeoSphere</td>
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<td>14.5 Treatment of Breast Cancer</td>
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<tr>
<td>TRYPHAENA</td>
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<td>(…) Randomization was stratified by the following factors: region, nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen. (…)</td>
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<td>14.6 Treatment of Breast Cancer</td>
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<td>(…) Consistent results were observed across several patient subgroups including age (&lt; 65 or 65 ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.96). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52). (…)</td>
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<td>NeoSphere</td>
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<tr>
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<td>(…) Clinical characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 49%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.96). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52). (…)</td>
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<td>14.7 Treatment of Breast Cancer</td>
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<tr>
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<td>(…) Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 49%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.96). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52). (…)</td>
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<tr>
<td>017473, 09/27/2011</td>
<td>Pimozide</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Precautions</td>
<td>dosage and administration of pimozide should be initiated at a dose of 8.8 mg/day, and titrated to a maximum dose of 17.8 mg once daily after 7 days. In patients known to be poor CYP2D6 metabolizers, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days (see Precautions - Pharmacogenomics).</td>
</tr>
<tr>
<td>018147, 05/03/2019</td>
<td>Piroxicam</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacogenomics 12.5 Pharmacogenomics CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9<em>2 and CYP2C9</em>3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/<em>2 (n=9), heterozygous CYP2C9</em>1/<em>3 (n=9), and homozygous CYP2C9</em>3/<em>3 (n=1) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9</em>1/<em>1 (n=17, normal metabolizer genotype) following administration of a single oral dose. The mean elimination half-life values of piroxicam for subjects with CYP2C9</em>1/<em>3 (n=9) and CYP2C9</em>3/<em>3 (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with CYP2C9</em>1/<em>1 (n=17). It is estimated that the frequency of the homozygous</em>3/*3 genotype is 0% to 1% in the population at large; however, frequencies as high as 6.7% have been reported in certain ethnic groups.</td>
</tr>
<tr>
<td>211150, 08/14/2019</td>
<td>Pitolisant</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.5 Use in Patients Who Are Known CYP2D6 Poor Metabolizers (PMs) In patients known to be poor CYP2D6 metabolizers, initiate WAKIX at 8.8 mg once daily and titrate to a maximum dose of 17.8 mg once daily after 7 days (see Use in Specific Populations (8.8), Clinical Pharmacology (12.5)).</td>
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The pharmacokinetics of pitolisant were evaluated in 3 subjects who were CYP2D6 poor metabolizers (PMs) and 5 subjects who were CYP2D6 extensive metabolizers (EMs). All subjects received WAKIX 17.8 mg daily for 7 days. Exposure of pitolisant in CYP2D6 PMs is summarized in Figure 3. (See Figure 3) 12.5 Pharmacogenomics
Approximately 3 to 10% of Caucasians and 2 to 7% of African Americans generally lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. The AUC of pitolisant was approximately 2.4 times higher in CYP2D6 poor metabolizers than in normal metabolizers and is similar to the exposure of pitolisant when WAKIX is administered concomitantly with a CYP2D6 inhibitor (see Dosage and Administration (2.5), Drug Interactions (7.7)).

In CYP2D6 poor metabolizers, the Cmax of pitolisant is 153 (151 to 157) ng/mL and the AUC is 1920 (1854 to 2000) ng*h/mL after steady state dosing with 35.6 mg once daily.

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<td>214701, 12/01/2020</td>
<td>Pralsetinib</td>
<td>Oncology</td>
<td>CCDC6-RET, KIF5B-RET, RET</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>One hundred and fifty-five of 449 patients (35%) in the clinical trial of iclucig 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 to patients &lt; 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 to patients &lt; 65 years of age (44%). (…)</td>
</tr>
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</table>

14 CLINICAL STUDIES
The safety and efficacy of iclucig in patients with CML and 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 iclucig 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 [Ph+ ALL]), resistance to 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, and 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 (MaHR), 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) (…) At the time of analysis, there were 133 patients ongoing (110 patients with CP-CML; 20 patients with AP-CML; 3 patients with BP-CML; 0 patients with Ph+ ALL), and the median duration of iclucig treatment was 32.2 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. (See Table 12 and 13) (…) The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 0.7 months (range: 0.4 to 5.8 months), 1.0 month (range 0.4 to 3.7 months), and 2.7 months (range: 0.4 to 5.5 months), respectively. The median duration of MaHR for patients with AP-CML, BP-CML, and Ph+ ALL was 12.6 months (range: 1.2 to 52+ months), 6.0 months (range: 1.8 to 47.4+ months), and 3.2 months (range: 1.8 to 12.8+ months), respectively.

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<td>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 (14.2, 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.</td>
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<td>RET-altered Thyroid Cancer</td>
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<td>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.</td>
</tr>
</tbody>
</table>

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 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. Cardiac Electrophysiology
The QT 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, non-randomized, 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-naive patients with metastatic NSCLC. Identification of a RET gene fusion was determined by local laboratories using standard methodologies, next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. Among the 114 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 (O DxTT). 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 400 mg 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 66 years (range: 28 to 85); 49% were female, 55% were White, 35% were Asian, 6% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%), 99% of patients had metastatic disease, and 43% had either a history of or current CNS metastasis. Among the 87 patients in the efficacy population(s), the median age was 66 years (range 30 to 87); 52% were female, 56% were White, 33% were Asian, 3% were Hispanic or Latino. ECOG performance status was 0-1 for 96% of the patients and all patients (100%) had metastatic disease. Among the 87 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.

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). Patients with RET fusion-positive MTC were previously treated with cabozantinib or vandetanib (or both). The median age was 59 years (range: 25 to 83); 69% were male, 78% were White, 5% were Asian, 5% were Hispanic/Latino. ECOG performance status was 0-1 (85%) or 2 (5%), and...
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| 022307, 03/28/2019                     | Prasugrel (1) | Cardiology | CYP2C19 | 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 (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. |

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<th>Labeling Text</th>
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<tbody>
<tr>
<td>022307, 03/28/2019</td>
<td>Prasugrel (4)</td>
<td>Cardiology</td>
<td>CYP2B6</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>(...) There is, however, an alternative explanation: both prasugrel and clopidogrel are prodrugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…)</td>
</tr>
</tbody>
</table>
| 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 adequate 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).

In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine.
If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available.
When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine.
Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available.
Discontinue the use of primaquine phosphate promptly if signs suggestive of hemolytic anemia occur (darkening of the urine, marked fall of hemoglobin or erythrocytic count).
Hemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia, and Oceania. People from these regions have a greater tendency to develop hemolytic anemia (due to a congenital deficiency of erythrocytic G6PD) while receiving primaquine and related drugs.

**Usage in Pregnancy**
Safe usage of this preparation in pregnancy has not been established. Primaquine is contraindicated in pregnant women. Even if a pregnant woman is G6PD normal, the fetus may not be (see Contraindications).

**PRECAUTIONS**

**Blood Monitoring**
Since anemia, 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>008316, 06/22/2017</th>
<th>Primaquine (2)</th>
<th>Infectious Diseases</th>
<th>CYP2B6</th>
<th>Precautions, Adverse Reactions</th>
<th>PRECAUTIONS</th>
</tr>
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<td>007898</td>
<td>Procainamide</td>
<td>Cardiology</td>
<td>G6PD</td>
<td>Adverse Reactions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<tr>
<td>020545</td>
<td></td>
<td></td>
<td></td>
<td>Clinical Pharmacology</td>
<td>Labeling not electronically available on Drugs@FDA</td>
</tr>
</tbody>
</table>
| 021418, 11/02/2018                     | Propranolol         | Cardiology      | CYP2D6    | Dosage and Administration | (...) If primaquine phosphate is prescribed for an individual who has shown a previous idiosyncratic reaction to primaquine phosphate as manifested by hemolytic anemia, methemoglobinemia, or leukopenia; an individual with a family or personal history of hemolytic anemia or nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency, the person should be observed closely. In all patients, the drug should be discontinued immediately if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs.  
ADVERSE REACTIONS  
Hematologic  
Leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.  
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.  
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.  
7 DRUG INTERACTIONS  
7.1 CYP2D6 and CYP3A4 Inhibitors  
Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline) and CYP3A4 (such as ketoconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be expected to cause increased plasma levels of propafenone. The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with administration of propafenone may increase the risk of adverse reactions, including proarrhythmia. Therefore, simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided [see Warnings and Precautions (5.4) and Dosage and Administration (2)].  
12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetic Metabolism  
There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (nonpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers. As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics is linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The larger inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity [see Dosage and Administration (2)]. Inter-Subject Variability.  
With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed |

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<td>Propranolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>following both single and multiple dose administration of RYTHMOL SR capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.</td>
</tr>
</tbody>
</table>
| 073644, 07/17/2014                     | Protriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS Drugs Metabolized by Cytochrome P450 2D6  
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine 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). |
| 089338, 02/02/2010                     | Quinine | Cardiology | CYP2D6 | Precautions | PRECAUTIONS  
(…) Constitutional deficiency of cytochrome P450IIID6 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 P450IIID6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers". When drugs whose metabolism is P450IIID6-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 prodrugs whose actions are actually mediated by P450IIID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive 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 P450IIID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IIID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IIID6. (…) |
| 021798, 06/19/2019                     | Quinine Sulfate (1) | Infectious Diseases | G6PD | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.3 Hemolytic Anemia  
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. |
| 021798, 06/19/2019                     | Quinine Sulfate (2) | Infectious Diseases | CYP2D6 | Drug Interactions | 7 DRUG INTERACTIONS  
7.2 Effects of Quinine on the Pharmacokinetics of Other Drugs  
Desipramine (CYP2D6 substrate)  
Quinidine (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. (…) |
| 020973, 06/07/2018                     | Rabeprazole | Gastroenterology | CYP2C19 | Drug Interactions, Clinical Pharmacology | 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)  
12 CLINICAL PHARMACOLOGY  
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. |
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</table>
| 020815, 06/27/2018                     | Ramucirumab (1) | Oncology | ESR (Hormone Receptor) | Clinical Studies | **14 CLINICAL STUDIES**

**14.3 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis**

CORE Trial

The effect of EVISTA on the incidence of invasive breast cancer was assessed in a secondary safety endpoint in a randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women [see Clinical Studies (14.1)]. After 4 years, EVISTA, 60 mg administered once daily, reduced the incidence of breast cancers by 62%, compared with placebo (HR 0.36, 95% CI 0.22-0.67). EVISTA reduced the incidence of invasive breast cancer by 71%, compared with placebo (ARR 3.1 per 1000 women-years); this was primarily due to an 80% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. (See Table 7)

**12 CLINICAL PHARMACOLOGY**

**12.5 Pharmacogenomics**

**UGT1A1 Polymorphism**

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult subjects with "*C*/*C" genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09). In the neonatal study IMPAACT P1110, there was no association between apparent clearance (CL/F) of raltegravir and UGT 1A1 genotype polymorphisms.

**Indications and Usage**

**1.2 Non-Small Cell Lung Cancer**

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 the treatment of 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.

**2 DOSAGE AND ADMINISTRATION**

**2.3 Recommended Dosage for Non-Small Cell Lung Cancer**

EGFR Exon 19 Deletions or Exon 21 (L858R) Substitution Mutations – CYRAMZA in Combination with Erlotinib

- The recommended dosage of CYRAMZA is 10 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity.
- Refer to the prescribing information for erlotinib for dosage information.

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

**Non-Small Cell Lung Cancer**

The safety of CYRAMZA was evaluated in RELAY [see Clinical Studies (14.2)]. Patients had previously untreated EGFR exon 19 deletion or exon 21 (L858R) substitution mutation-positive metastatic NSCLC. (…)

**14 CLINICAL STUDIES**

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<tr>
<td>103946, 12/12/2019</td>
<td>Rasburicase (1)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING WARNING: HYPERSENSITIVITY ReACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASEUREMENTS 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).</td>
</tr>
<tr>
<td>103946, 12/12/2007</td>
<td>Rasburicase (2)</td>
<td>Oncology</td>
<td>CYB5R</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING WARNING: HYPERSENSITIVITY ReACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASEUREMENTS Methemoglobinemia Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek if methemoglobinemia occurs (4, 5.3).</td>
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<td>Ribociclib</td>
<td>Oncology</td>
<td>ESR, PGR</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Hormone Receptor)</td>
<td></td>
<td>1.1 Colorectal Cancer</td>
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<tr>
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<td></td>
<td></td>
<td>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>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Colorectal Cancer</td>
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<td>(….) Baseline demographics were: median age 61 years, 61% men, 78% White, and all patients had an ECOG performance status of 0 or 1. The primary sites of disease were colon (65%), rectum (29%), or both (9%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. 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/negative tumors received panitumumab or cetuximab. (….)</td>
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<tr>
<td>209092, 01/21/2020</td>
<td>Ribociclib</td>
<td>Oncology</td>
<td>ERBB2</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td></td>
<td>(HER2)</td>
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<td>KISQALI is indicated in combination with:</td>
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<td>• 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</td>
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<td>• 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.</td>
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| 212728, 02/27/2020                      | Rimegepant | Anesthesiology | CYP2C9     | Clinical Pharmacology | The safety data reported below are based on MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥12 months. (…)
|                                        |      |                   |            |                   |               |
| 213535, 08/07/2020                      | Risdiplam | Neurology         | SMN1, SMN2 | Clinical Studies  | 14 CLINICAL STUDIES
|                                        |      |                   |            |                   |               |
| 020272, 01/25/2019                      | Risperidone | Psychiatry       | CYP2D6     | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
|                                        |      |                   |            |                   |               |

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| 103705, 03/13/2020                    | Ritu

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 risperidone to 9-hydroxyrisperidone (see Drug Interactions (7)). This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The pharmacokinetic and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number of patients (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 concentrations of risperidone and 9-hydroxyrisperidone (see Drug Interactions (7)). It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (see Drug Interactions (7)).

**Excretion**

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

**1 INDICATIONS AND USAGE**

**1.1 Non–Hodgkin’s Lymphoma (NHL)**

Rituximab (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.
- Previously untreated diffuse large B-cell, CD20-negative NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

**1.2 Chronic Lymphocytic Leukemia (CLL)**

Rituximab (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 Doses for Non-Hodgkin’s Lymphoma (NHL)**

The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:

- Administer once weekly for 4 or 8 doses.
- Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.
- Previously untreated, follicular, CD20-positive, B-cell NHL
- Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy.
- 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.

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience in Lymphoid Malignancies**

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**

**8.5 Geriatric Use**

Low-Grade or Follicular Non-Hodgkin’s Lymphoma

Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

**14 CLINICAL STUDIES**

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<td>02/24/06, 01/15/2019</td>
<td>Rivaroxaban</td>
<td>Cardiology</td>
<td>F5 (Factor V Leiden)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td></td>
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<td></td>
<td>14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients. (…)</td>
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<td>02/05/33, 11/02/2018</td>
<td>Ropivacaine (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>
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<tr>
<td>02/05/33, 11/02/2018</td>
<td>Ropivacaine (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>
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<td>02/1369, 11/09/2018</td>
<td>Rosuvastatin</td>
<td>Endocrinology</td>
<td>SLCO1B1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Disposition of HMGC-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 (SLCO1B1 52T&gt;C). The frequency of this genotype (i.e., SLCO1B1 52T&gt;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.</td>
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<tr>
<td>209115, 10/08/2020</td>
<td>Rucaparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>1 INDICATIONS AND USAGE 1.1 Ovarian Cancer • Rubraca is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. • Rubraca is indicated for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca [see Dosage and Administration (2.1)]. 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 with 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. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Treatment of BRCA-mutated Ovarian Cancer after 2 or More Chemotherapies Select patients for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer with Rubraca based on the presence of a deleterious BRCA mutation (germline and/or somatic) [see Clinical Studies (14.1)]. 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 genomic 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>. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience</td>
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<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Treatment of BRCA-mutated Recurrent Ovarian Cancer After 2 or More Chemotherapies. (…) Rucaparib 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had BRCA-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197). (…) Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy. The safety of Rucaparib 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 Rucaparib treatment was 6.5 months (range 0.5 to 26.7). (…) Tables 6 and 7 summarize the adverse reactions and laboratory abnormalities, respectively, in patients with BRCA-mutated mCRPC in TRITON2. (See Tables 6 and 7) (…).</td>
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</table>
| Rucaparib (3) | Oncology | CYP1A2 | Clinical Pharmacology | 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=584), 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 (BRCA) mutant status was confirmed by the FoundationFocus™ CDx BRCA LOH test for 98% (177/179) of BRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the BRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the BRCA 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 Rucaparib as compared with placebo in all patients, and in the HRD and BRCA 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 Rucaparib was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 10 (NCT01891344), in patients with advanced BRCA-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rucaparib 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and IRR according to RECIST v1.1. The median age of the patients was 59 years (range: 33 to 84), the majority were White (78%), and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had received 3 or more prior lines of platinum-based chemotherapy. There were 18/106 patients (17%) who had deleterious BRCA mutations detected in tumor tissue and not in whole blood specimens. Tumor BRCA mutation status was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available. The companion diagnostic FoundationFocus™ CDxBRCA test, which is FDA approved for selection of patients for Rucaparib treatment. (See Table 9)  
Response assessment by independent radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). Investigator-assessed ORR was 66% (52/79; 95% CI [84, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation. |
| Rucaparib (4) | Oncology | BRCA, Loss of Heterozygosity | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia  
Rucaparib 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had BRCA-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197). (…) Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy. The safety of Rucaparib 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 Rucaparib treatment was 6.5 months (range 0.5 to 26.7). (…) Tables 6 and 7 summarize the adverse reactions and laboratory abnormalities, respectively, in patients with BRCA-mutated mCRPC in TRITON2. (See Tables 6 and 7) (…)  
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| **761115, 04/22/2020** | Satralizumab | Neurology | UG1TA1 | Warnings and Precautions, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS
5.5 Use in Patients with Reduced UG1TA1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronyltransferase 1A1 (UG1TA1)*2 allele are at increased risk for neutropenia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment. In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UG1TA1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/38) in patients homozygous for the UG1TA1*2 allele, 13% (20/155) in patients heterozygous for the UG1TA1*2 allele and 11% (16/149) in patients homozygous for the wild-type allele (Clinical Pharmacology (12.5)). Closely monitor patients with reduced UG1TA1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UG1TA1*2 is not known and should be considered based on individual patient tolerance to treatment (see Dosage and Administration (2.3)). |
| **761149, 06/14/2020** | Satralizumab | Neurology | AQP4 | Indications and Usage, Adverse Reactions, Clinical Studies | 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. |

**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 (14.5)]. In both studies, 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. |

### 14 CLINICAL STUDIES
The efficacy of ENSPRYNG for the treatment of NMOSD in adult patients was established in two studies. Study 1 was a randomized (2:1), placebo-controlled trial in 96 patients without concurrent IST (Study 1, NCT02073279) in which 64 patients were anti-AQP4 antibody positive and 32 patients were anti-AQP4 antibody negative. Study 2 was a randomized (1:1), placebo-controlled trial in 76 adult patients with concurrent IST (Study 2, NCT02028884). Of these, 52 adult patients were anti-AQP4 antibody positive and 24 adult patients were anti-AQP4 antibody negative. |

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<td>213246, 05/08/2020</td>
<td>Selpercatinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>In Study 1, 41 anti-AQP4 antibody positive adult patients were randomized to and received ENSPRYNG and 23 received placebo. Females accounted for 78% of the ENSPRYNG group and 98% of the placebo group. The remaining baseline demographic characteristics were balanced between the treatment groups. The mean age was 44 years. Fifty percent were White, 22% were Black or African-American, and 20% were Asian. The mean EDSS score was 3.8. In Study 2, 26 anti-AQP4 antibody positive adult patients were randomized to and received ENSPRYNG and 26 received placebo. All patients were receiving either concurrent azathioprine (42%), oral corticosteroids (52%), or mycophenolate mofetil (6%) during the trial. The baseline demographic and disease characteristics were balanced between the treatment groups. Females accounted for 100% of the study population. Forty-six percent of patients were White and 52% were Asian. The mean age was 46 years. The mean EDSS score was 4.0. All potential relapses were adjudicated by a blinded Clinical Endpoint Committee (CEC). The primary efficacy endpoint for both studies was the time to the first CEC-confirmed relapse. In Study 1, the time to the first CEC-confirmed relapse was significantly longer in ENSPRYNG treated patients compared to patients who received placebo (risk reduction 53%, hazard ratio 0.46, p = 0.0184). In the anti-AQP4 antibody negative population, there was a 74% risk reduction; hazard ratio 0.26, p = 0.0014. There was no evidence of a benefit in the anti-AQP4 antibody positive patients. In Study 2, the time to the first CEC-confirmed relapse was significantly longer in patients treated with ENSPRYNG compared to patients who received placebo (risk reduction 62%, hazard ratio 0.38, p = 0.0184). In the anti-AQP4 antibody positive population, there was a 78% risk reduction; hazard ratio 0.22, p = 0.0143. There was no evidence of a benefit in the anti-AQP4 antibody negative patients. (See Table 5 and Figures 1 and 2.)</td>
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<td>Sevoflurane</td>
<td>Anesthesiology</td>
<td>RYR1</td>
<td>Warnings</td>
<td>Malignant Hyperthermia In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Sevoflurane can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypocapnia, and hyperventilation. In clinical trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these cases have been fatal.</td>
</tr>
</tbody>
</table>

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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: 12/2020

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<thead>
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<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>
</table>
| 213793, 11/25/2020                     | Setmelanotide (1) | Endocrinology | LEPR       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS). 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

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
- Select patients for treatment with IMCIVREE who have genetically confirmed 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 [see Clinical Studies (14)].
- Currently available tests for the detection of variants in the POMC, PCSK1, or LEPR genes have not been approved or cleared by the FDA

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. 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 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 either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not eligible for IMCIVREE treatment and 1 was positive pretreatment. None of the patients with POMC-deficiency were confirmed to have antibodies to alpha-MSH. (…)

6.2 Immunogenicity
(…)
Approximately 61% of adult and pediatric patients with POMC- or LEPR-deficiency who received IMCIVREE (N=28) screened positive for antibodies to IMCIVREE and 36% 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 for obesity due to POMC, PCSK1, or LEPR deficiency have been established in pediatric patients aged 6 years and older. Use of IMCIVREE for this indication is supported by evidence from 2 open-label studies that included 9 pediatric patients [see Clinical Studies (14)]. The safety and effectiveness of IMCIVREE have not been established in pediatric patients younger than 6 years old.

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 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency. Study 2 (NCT03287960) enrolled patients aged 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 either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not eligible for treatment with IMCIVREE. In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m². Weight in pediatric patients was 95th percentile using growth chart assessments. 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).
### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2020**

| NDA/ANDA/BLA Number, Label Version Date | Drug | Therapeutic Area† | Biomarker‡ | Labeling Sections | Labeling Text
|--------------------------------------|------|-------------------|------------|-----------------|----------------|
| 213793, 11/25/2020                    | Setmelanotide (3) | Endocrinology | POMC | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | • Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polycgenic) obesity

#### 2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

- Select patients for treatment with IMCIVREE who have genetically confirmed 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)).
- Currently available tests for the detection of variants in the POMC, PCSK1, or LEPR genes have not been approved or cleared by the FDA

#### 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 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)).

#### 8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of IMCIVREE have not been established in pediatric patients younger than 6 years old.

#### 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 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT02879660) enrolled patients aged 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 either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not eligible for treatment with IMCIVREE. In both studies, adult patients had a body mass index (BMI) of 35 kg/m².

#### 16 CLINICAL STUDIES

In Study 1, 86% of patients with obesity due to POMC or PCSK1 deficiency achieved 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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| 205123, 11/09/2017                | Simeprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology, Clinical Studies | 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 for obesity due to POMC, PCSK1, or LEPR deficiency have been established in pediatric patients aged 6 years and older. Use of IMCIVREE for this indication is supported by evidence from 2 open-label studies that included 9 pediatric patients [see Clinical Studies (14)]. The safety and effectiveness of IMCIVREE have not been established in pediatric patients younger than 6 years old.

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 (NCT02896612) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT03297960) enrolled patients aged 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 either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not eligible for treatment with IMCIVREE. In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m². Weight in pediatric patients was ≥95th percentile using growth chart assessment.

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)

14 CLINICAL STUDIES

14.2 OLYSIO in Combination with Sofosbuvir

Adolescents 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 6.7 log10 IU/mL; 19%, 31%, and 22% had METAVIR fibrosis score F0-F1, F2 and F3, respectively, and 29% had HCV genotype 1a of which 41% carried Q80K at baseline, and 25% had HCV genotype 1b; 14% had IL28B CC genotype, 64% IL28B CT genotype, and 22% IL28B TT genotype; 75% were prior null responders to Peg-IFN-alfa and RBV, and 25% were treatment-naive.

OPTIMIST-1 was an open-label, randomized Phase 3 trial in HCV genotype 1-infected subjects without cirrhosis who were treatment-naive or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred five subjects received 12 weeks of OLYSIO with sofosbuvir had a median age of 56 years (range 19 to 70 years; with 7% above 65 years); 53% were male; 78% were White, 20% Black or African American, and 16% Hispanic; 37% had a BMI ≥ 30 kg/m²; the median baseline HCV RNA level was 8.8 log10 IU/mL; 75% had HCV genotype 1a of which 40% had Q80K polymorphism at baseline and 25% had HCV genotype 1b; 55% had IL28B TT genotype; 29% had IL28B CC genotype, 55% IL28B CT genotype, and 22% IL28B TT genotype; 74% were treatment-naive and 26% were treatment-experienced. (…)

(…) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subjects, including: treatment-naive (104/105 [99%] and 38/38 [100%] 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 (43/43 [100%] and 107/112 [96%], respectively).

14.3 OLYSIO in Combination with Peg-IFN-alfa and RBV

Treatment-Naive 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. In the pooled analysis of trials (QUEST 1 and QUEST 2), the 785 enrolled subjects had a median age of 47 years (range: 18 to 73 years; with 2% above 65 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; 75% had baseline HCV RNA levels greater than 80000 IU/mL; 74% had METAVIR fibrosis score F0, F1 or F2; 16% METAVIR fibrosis score F3, and 10% METAVIR fibrosis score F4 (cirrhosis); 48% had HCV genotype 1a, and 51% HCV genotype 1b; 29% had IL28B CC genotype, 56% IL28B CT genotype, and 15% IL28B TT genotype; 75% 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, 66% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b.

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</table>
| 03/26/2019  | 209884        |                     | Siponimod | Neurology | CYP2C9   | Dosage and Administration, Contraindications, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.1 Assessments Prior to First Dose of MAYZENT
Before initiation of treatment with MAYZENT, the following assessments should be performed: CYP2C9 Genotype Determination
Test patients for CYP2C9 variants to determine CYP2C9 genotype [see Dosage and Administration (2.2, 2.3), Contraindications (4), and Use in Specific Populations (8.6)]. An FDA-cleared or approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available.
2.2 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2
Maintenance Dosage
After treatment initiation (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 2 mg taken orally once daily starting on Day 6. Dosage adjustment is required in patients with a CYP2C9 *1/*1 or *1/*2 genotype [see Dosage and Administration (2.3)]. Treatment Initiation
Initiate MAYZENT with a 5-day titration, as shown in Table 1 [see Warnings and Precautions (5.3)]. A starter pack should be used for patients who will be titrated to the 2-mg maintenance dosage [see How Supplied/Storage and Handling (16.1, 16.2)]. If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.
2.2 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3

| Table 17 shows the response rates in treatment-naive adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR24 rates were lower in subjects with genotype 1a virus than the NS5B Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. (See Table 17) (…)
| Table 18 shows the response rates in treatment-naive East Asian subjects with HCV genotype 1 infection. (…)

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<tbody>
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<td>Maintenance Dosage</td>
<td>In patients with a CYP2C9 *1/*3 or *2/*3 genotype, after treatment titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 6. Treatment Initiation. Initiate MAYZENT with a 4-day titration, as shown in Table 2 (see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)). Do not use the starter pack for patients who will be titrated to the 1-mg maintenance dosage. (See Table 2.) If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.</td>
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<td>4 CONTRAINDICATIONS</td>
<td>MAYZENT is contraindicated in patients who have:</td>
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<td>• A CYP2C9*3/*3 genotype (see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)) (…)</td>
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<td>7 DRUG INTERACTIONS</td>
<td>7.6 CYP2C9 and CYP3A4 Inducers</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.2 Pharmacodynamics</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Coadministration of Siponimod with CYP2C9 and CYP3A4 Inhibitors</td>
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<td>12.5 Pharmacogenomics</td>
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<tbody>
<tr>
<td>203922, 10/19/2017 Sodium Nitrite (1)</td>
<td>Toxicology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>The CYP2C9 genotype has a significant impact on siponimod metabolism. After a single dose of 0.25 mg siponimod, AUCl2 and AUCl6 were approximately 2- and 4-fold higher in subjects with the CYP2C9*2/<em>3 and CYP2C9</em>3/<em>3 genotypes, respectively, while there was only a minor increase in CYP2C9</em>1/<em>1. Metabolite half-life is prolonged in CYP2C9</em>2/<em>3 and CYP2C9</em>3/<em>3 carriers (0.1 hours and 126.8 hours, respectively). An apparent systemic clearance (CL/F) of about 3.1 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9</em>1/<em>1 and CYP2C9</em>1/<em>2) M6 patients after multiple oral administrations of siponimod. CL/F is 2.5, 1.9, 1.6, and 0.9 L/h in subjects with the CYP2C9</em>2/<em>2, CYP2C9</em>1/<em>3, CYP2C9</em>2/<em>3, and CYP2C9</em>3/<em>3 genotypes, respectively. The resultant increase in siponimod AUC was approximately 25, 61, 91, and 285% higher in CYP2C9</em>2/<em>2, CYP2C9</em>1/<em>3, CYP2C9</em>2/<em>3, and CYP2C9</em>3/<em>3 subjects, respectively, as compared to CYP2C9</em>1/<em>1 subjects. As the apparent clearance estimated for CYP2C9</em>1/<em>2 subjects is comparable to that of CYP2C9</em>1/*1 subjects, similar siponimod exposure is expected for both genotypes.</td>
<td></td>
</tr>
<tr>
<td>203922, 10/19/2017 Sodium Nitrite (2)</td>
<td>Toxicology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Boxed Warning, Warnings and Precautions</td>
<td>BOXED 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 the 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., smoke inhalation victims, pre-existing anemia, cardiac or respiratory compromise), and those at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency). As the apparent clearance estimated for CYP2C9*1/<em>2 subjects is comparable to that of CYP2C9</em>1/*1 subjects, similar siponimod exposure is expected for both genotypes.</td>
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<td>The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450–600 mg/kg/day in patients weighing less than 20 kg, or 9.9–13.0 g/m2/day in larger patients. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day). (…)</td>
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</table>

**NUTRITIONAL MANAGEMENT**

(…) At the recommended dose of sodium phenylbutyrate, it is suggested that infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period. Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake. From 4 months to 1 year of age, it is recommended that the infant receive at least 1.4 g/kg/day, but 1.7 g/kg/day is advisable. From 1 to 3 years of age, the protein intake should not be less than 1.2 g/kg/day; 1.4 g/kg/day is advisable during this period. For neonatal-onset patients with carbamylphosphate synthetase deficiency or ornithine transcarbamylase deficiency who are at least 6 months of age, it is recommended that the daily protein intake be equally divided between natural protein and supplemental essential amino acids.

Patients with argininosuccinic acid synthetase deficiency and those with late-onset disease (partial deficiencies, including females heterozygous for ornithine transcarbamylase), initially may receive a diet containing the age-determined minimal daily natural protein allowance. The protein intake may be increased as tolerated and determined by plasma glutamine and other amino acid levels. However, many patients with partial deficiencies avoid dietary protein. Citrulline supplementation is required and recommended for patients diagnosed with neonatal-onset deficiency of carbamylphosphate synthetase or ornithine transcarbamylase; citrulline daily intake is recommended at 0.17 g/kg/day or 3.8 g/m2/day. (…) The free-base form of arginine may be used instead of citrulline in patients with milder forms of carbamylphosphate synthetase and ornithine transcarbamylase deficiency (daily intake is recommended at 0.17 g/kg/day or 3.8 g/m2/day). Arginine supplementation is needed for patients diagnosed with deficiency of argininosuccinic acid synthetase; arginine (free base) daily intake is recommended at 0.4–0.7 g/kg/day or 8.8–15.4 g/m2/day. |  |

### 204671

<table>
<thead>
<tr>
<th>10/23/2018</th>
<th>Sofosbuvir</th>
<th>Infectious Diseases</th>
<th>IFNL3 (IL28B)</th>
<th>Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2 CLINICAL STUDIES</td>
<td>Sofosbuvir in Subjects with Genotype 1 or 4 HCV</td>
<td>Treatment-Naive Adults ─ NEUTRINO (Study 110)</td>
<td>(…) SVR12 rates were 99% (89/90) in subjects with genotype 1 or 4 HCV and baseline IL28B C/C allele and 87% (200/230) in subjects with genotype 1 or 4 HCV and baseline IL28B non-C/C alleles. It is estimated that the SVR12 in patients who previously failed pegylated interferon and ribavirin therapy will approximate the observed SVR12 in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment (Table 9). The SVR12 rate in the NEUTRINO trial in genotype 1 subjects with IL28B non-C/C alleles, HCV RNA greater than 800,000 IU/mL, and Metavir F3/F4 fibrosis was 71% (37/52). (See Table 9)</td>
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<tr>
<td>14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1</td>
<td>(…) in subjects with HCV genotype 1 infection, the SVR12 rate was 82% (74/90) in subjects with genotype 1a infection and 54% (13/24) in subjects with genotype 1b infection, with relapse accounted for the majority of treatment failures. SVR12 rates in subjects with HCV genotype 1 infection were 80% (24/30) in subjects with baseline IL28B C/C allele and 75% (62/83) in subjects with baseline IL28B non-C/C alleles.</td>
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<tr>
<td>14.6 Clinical Trial in Pediatrics</td>
<td>The efficacy of SOVALDI in HCV-infected pediatric subjects 12 years of age and older was evaluated in 50 subjects with HCV genotype 2 (N = 13) or genotype 3 (N = 37) in a Phase 2, open-label clinical trial. Subjects with HCV genotype 2 or 3 infection in the trial were treated with SOVALDI and weight-based ribavirin for 12 or 24 weeks, respectively [see Dosage and Administration (2.3)].</td>
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### 208341

<table>
<thead>
<tr>
<th>11/09/2017</th>
<th>Sofosbuvir and Velpatasvir</th>
<th>Infectious Diseases</th>
<th>IFNL3 (IL28B)</th>
<th>Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2 CLINICAL STUDIES</td>
<td>Sofosbuvir and Velpatasvir in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis</td>
<td>Genotype 1, 2, 4, 5, and 6 HCV Infected Adults (ASTRAL-1)</td>
<td>(…) Demographics and baseline characteristics were balanced between the EPCLUSA and placebo group. Of the 740 treated subjects, the median age was 56 years (range: 18 to 82); 60% of the subjects were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 61 kg (range: 36 to 101 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 80,000 IU/mL; 74% of subjects had non-CC IL28B alleles (CT or TT); and no subjects had known cirrhosis. The majority of subjects (69%) had been infected through vertical transmission. Of the 50 treated subjects, the median age was 15 years (range: 12 to 17); 42% of the subjects were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 61 kg (range: 36 to 101 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 80,000 IU/mL; 74% of subjects had non-CC IL28B alleles (CT or TT); and no subjects had known cirrhosis.</td>
<td></td>
</tr>
<tr>
<td>14.3 Clinical Trial in Subjects Coinfected with HCV and HIV-1</td>
<td>(…) In subjects with HCV genotype 1 infection, the SVR12 rate was 82% (74/90) in subjects with genotype 1a infection and 54% (13/24) in subjects with genotype 1b infection, with relapse accounted for the majority of treatment failures. SVR12 rates in subjects with HCV genotype 1 infection were 80% (24/30) in subjects with baseline IL28B C/C allele and 75% (62/83) in subjects with baseline IL28B non-C/C alleles.</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2020**

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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>
</tr>
</thead>
</table>
| 209195, 11/09/2017 | 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. (…) |
| 019998, 10/02/2018 | Succinylocholine | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14.4 clinical trials in subjects with decompensated cirrhosis
(…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 24 to 85); 77% of the subjects were male; 87% were White, 9% were Black; 8% were Hispanic or Latino; 35% had a baseline body mass index of at least 30 kg/m²; the majority of subjects had genotype 1, 2, 3, 4, or 6 HCV RNA levels at least 800,000 IU/mL; and 41% had compensated cirrhosis. (…) |
| 008453, 07/26/2018 | Succinylocholine | Anesthesiology | BCHE | Warnings, Precautions | WARNINGS
(…) Succinylocholine is metabolized by plasma cholinesterase and should be used with caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene. |
| 008453, 07/26/2018 | Succinylocholine | Anesthesiology | Non-specific (Genetic Susceptibility to Malignant Hyperthermia) | Boxed Warning, Contraindications, Warnings, Precautions, Adverse Reactions | WARNING
RISK OF CARDIAC ARREST FROM HYPERKALEMIC RHABDOMYOLYSIS
There have been rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrythmias, cardiac arrest, and death after the administration of succinylocholine to apparently healthy pediatric patients who were subsequently found to have undiagnosed skeletal muscle myopathy, most frequently Duchenne's muscular dystrophy. This syndrome often presents as peaked T-waves and sudden cardiac arrest within minutes after the administration of the drug is healthy appearing pediatric patients (usually, but not exclusively, males, and most frequently 8 years of age or younger). There have also been reports in adolescents. Therefore, when a healthy appearing infant or child develops cardiac arrest soon after administration of succinylocholine not felt to be due to inadequate ventilation, oxygenation, or anesthetic overdose, immediate treatment for hyperkalemia should be instituted. This should include administration of intravenous calcium, bicarbonate, and glucose with insulin, and hormone. Due to the abrupt onset of this syndrome, routine resuscitative measures are likely to be unsuccessful. However, extraordinary and prolonged resuscitative efforts have resulted in successful resuscitation in some reported cases. In addition, in the presence of signs of malignant hyperthermia, appropriate treatment should be instituted concurrently. Since there may be no signs or symptoms to alert the practitioner to which patients are at risk, it is recommended that the use of succinylocholine in pediatric patients should be reserved for emergency intubation or instances where immediate securing of the airway is necessary, e.g., laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible (see PRECAUTIONS: Pediatric Use and DOSAGE AND ADMINISTRATION). |

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<tbody>
<tr>
<td>017381, 08/01/2016</td>
<td>Sulfadiazine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings</td>
<td>Succinylcholine is contraindicated in persons with personal or familial history of malignant hyperthermia, skeletal muscle myopathies, and known hypersensitivity to the drug. It is also contraindicated in patients after the acute phase of injury following major burns, multiple trauma, extensive denervation of skeletal muscle, or upper motor neuron injury, because succinylcholine administered to such individuals may result in severe hyperkalemia which may result in cardiac arrest (see WARNINGS). The risk of hyperkalemia in these patients increases over time and usually peaks at 7 to 10 days after the injury. The risk is dependent on the extent and location of the injury. The precise time of onset and the duration of the risk period are not known.</td>
</tr>
<tr>
<td>017377, 07/16/2014</td>
<td>Sulfamethoxazole and Trimethoprim (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions</td>
<td>Succinylcholine administration has been associated with acute onset of malignant hyperthermia, a potentially fatal hypermetabolic state of skeletal muscle. The risk of developing malignant hyperthermia following succinylcholine administration increases with the concomitant administration of volatile anesthetics. Malignant hyperthermia frequently presents as intractable spasm of the jaw muscles (masseter spasm) which may progress to generalized rigidity, increased oxygen demand, tachycardia, tachypnea, and profound hyperpyrexia. Successful outcome depends on recognition of early signs, such as jaw muscle spasm, acidosis, or generalized rigidity to initial administration of succinylcholine for tracheal intubation, or failure of tachycardia to respond to deepening anesthesia. Skin flushing, rising temperature, and coagulopathies may occur later in the course of the hypermetabolic process. Recognition of the syndrome is a signal for discontinuance of anesthesia, attention to increased oxygen consumption, correction of acidosis, support of circulation, assurance of adequate urinary output, and institution of measures to control rising temperature. Intravenous dantrolene sodium is recommended as an adjunct to supportive measures in the management of this problem. Consult literature references and the dantrolene prescribing information for additional information about the management of malignant hyperthermia crisis. Continuous monitoring of temperature and expired CO2 is recommended as an aid to early recognition of malignant hyperthermia.</td>
</tr>
<tr>
<td>017377, 07/16/2014</td>
<td>Sulfamethoxazole and Trimethoprim (2)</td>
<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Precautions</td>
<td>Succinylcholine causes profound muscle relaxation resulting in respiratory depression to the point of apnea; this effect may be prolonged. Hypersensitivity reactions, including anaphylaxis, may occur in rare instances. The following additional adverse reactions have been reported: cardiac arrest, malignant hyperthermia, arrhythmias, bradycardia, tachycardia, hypertension, hypotension, hyperkalemia, prolonged respiratory depression or apnea, increased intracranial pressure, muscle fasciculation, jaw rigidity, hypotensive muscle pain, rhabdomyolysis with possible myoglobinuric acute renal failure, excessive salivation, and rash.</td>
</tr>
<tr>
<td>007073, 03/04/2014</td>
<td>Sulfasalazine (1)</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>Hemolysis In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see Clinical Pharmacology and Dosage and Administration).</td>
</tr>
<tr>
<td>007073, 03/04/2014</td>
<td>Sulfasalazine (2)</td>
<td>Gastroenterology</td>
<td>Nonspecific (NAT)</td>
<td>Precautions</td>
<td>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 anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, AZULFIDINE EN-tabs should be discontinued immediately.</td>
</tr>
<tr>
<td>007073, 03/04/2014</td>
<td>Sulfasalazine (2)</td>
<td>Gastroenterology</td>
<td>Clinical Pharmacology</td>
<td></td>
<td>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 acetylate, 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-hydroxysulfapyridine (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 prolonging plasma half-life for 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.</td>
</tr>
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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 (5.1)].  
• 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 (3) | Gynecology | SERPIN1C1 (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. |
| 211996, 05/03/2019                     | Tafamidis | Cardiology | TTR | Clinical Pharmacology, Clinical Studies | 12. CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
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 tetramers 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) |
| 219607, 08/08/2018                     | Tafenoquine | Infectious Diseases | G6PD | Dosage and Administration, Contraindications, Warnings and Precautions | 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)].  
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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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<tr>
<td></td>
<td><strong>4 CONTRAINDICATIONS</strong></td>
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<td>ARAKODA is contraindicated in:</td>
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<td>• patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia [see Warnings and Precautions (5.2)];</td>
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<td>• 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)];</td>
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<td></td>
<td><strong>5 WARNINGS AND PRECAUTIONS</strong></td>
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<td>5.1. Hemolytic Anemia</td>
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<td>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.</td>
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<td></td>
<td>5.2 G6PD Deficiency in Pregnancy and Lactation</td>
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<tr>
<td></td>
<td><strong>Potential Harm to the Fetus</strong></td>
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<td>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 could 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].</td>
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<tr>
<td></td>
<td><strong>Potential Harm to the Breastfeeding Infant</strong></td>
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<td>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)].</td>
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<td></td>
<td><strong>8 USE IN SPECIFIC POPULATIONS</strong></td>
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<tr>
<td></td>
<td>8.1 Pregnancy Risk Summary</td>
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<td>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)].</td>
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<td>8.2 Lactation Risk Summary</td>
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<td></td>
<td>A breastfeeding 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.</td>
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<tr>
<td></td>
<td><strong>8.3 Females and Males of Reproductive Potential</strong></td>
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<tr>
<td></td>
<td><strong>Contraception</strong></td>
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<td></td>
<td>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.</td>
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<tr>
<td></td>
<td><strong>17 PATIENT COUNSELING INFORMATION</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>G6PD Testing and Hemolytic Anemia</strong></td>
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<tr>
<td></td>
<td>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)].</td>
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</tr>
<tr>
<td></td>
<td><strong>Lactation</strong></td>
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</tr>
<tr>
<td></td>
<td>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)].</td>
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<th>Labeling Sections</th>
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<td>021807,</td>
<td>04/08/2019</td>
<td>Tamoxifen</td>
<td>Oncology</td>
<td>ESR, PGR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>SOLTAMOX is indicated for the treatment of adult patients with estrogen receptor-positive metastatic breast cancer. (1)</td>
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<tr>
<td>211651,</td>
<td>03/09/2020</td>
<td>Talazoparib</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>TALZENNA is indicated for the treatment of adult patients with deleterious of suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Selected patients for therapy based on an FDA-approved companion diagnostic for TALZENNA (see Dosage and Administration (2.1)).</td>
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Anastrozole Adjuvant Trial (ATAC: Arimidex, Tamoxifen, Alone or in Combination) – Study of Anastrozole Compared to Tamoxifen for Adjuvant Treatment of Early Breast Cancer
At a median follow-up of 5.3 years, the combination of anastrozole and tamoxifen did not demonstrate an efficacy benefit when compared to tamoxifen monotherapy in all patients. The combination treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 5.2 months and 5.6 months for patients receiving anastrozole 1 mg and tamoxifen 20 mg monotherapy, respectively. (…)

12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not 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 WHI (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
Postmenopausal women with hormone receptor-positive breast cancer were randomized to receive adjuvant treatment with either anastrozole 1 mg daily, another formulation of tamoxifen 20 mg daily, or a combination of these two treatments for 5 years or until recurrence of the disease. At a median follow-up of 33 months, the combination of anastrozole and tamoxifen did not demonstrate an efficacy benefit when compared to tamoxifen monotherapy, respectively. (…)

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<td>021807, 04/08/2019</td>
<td>Tamsulosin (2)</td>
<td>Urology</td>
<td>Cytochrome P450 2D6 (CYP2D6)</td>
<td>Warnings and Precautions</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., terbutaline) 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)]. 5.2 Thromboembolic Events 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 (8.22), 8.1 (44), and 5.6 (3.8) ng/mL in 27 ultrafast, 1097 normal, 164 intermediate, and 82 poor metabolizers, respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.</td>
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<tr>
<td>021807, 04/08/2019</td>
<td>Tamsulosin (3)</td>
<td>Oncology</td>
<td>Cytochrome P450 2D6 (CYP2D6)</td>
<td>Warnings and Precautions</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., terbutaline) 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)]. 5.2 Thromboembolic Events 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 (8.22), 8.1 (44), and 5.6 (3.8) ng/mL in 27 ultrafast, 1097 normal, 164 intermediate, and 82 poor metabolizers, respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.</td>
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<td>021807, 04/08/2019</td>
<td>Tamsulosin (4)</td>
<td>Oncology</td>
<td>Cytochrome P450 2D6 (CYP2D6)</td>
<td>Warnings and Precautions</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., terbutaline) 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)]. 5.2 Thromboembolic Events 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 (8.22), 8.1 (44), and 5.6 (3.8) ng/mL in 27 ultrafast, 1097 normal, 164 intermediate, and 82 poor metabolizers, respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.</td>
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<td>Tetrabenazine</td>
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<td>CYP2D6</td>
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<td>Administration, Warnings, Use in Specific Populations, Clinical Pharmacology</td>
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<td>Administration</td>
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<td>201917,</td>
<td>Telaprevir</td>
<td>Infectious</td>
<td>Clinical</td>
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<td>10/28/2013</td>
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<td>Diseases</td>
<td>Pharmacology, Clinical Studies</td>
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  - **Drug**: Tetrabenazine, Telaprevir
  - **Labeling Sections**: Neurology, Clinical Pharmacology
  - **Labeling Text**: CYP2D6, Clinical Pharmacology

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<td>012429, 05/23/2018</td>
<td>Thioguanine (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings, Precautions, Clinical Pharmacology</td>
<td>(…) Patients with homozygous 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 homozygous 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>012429, 05/23/2018</td>
<td>Thioguanine (2)</td>
<td>Oncology</td>
<td>NUDT15</td>
<td>Dosage and Administration, Warnings, Precautions, Clinical Pharmacology</td>
<td>(…) Patients with homozygous 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 homozygous 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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<td>Ticagrelor</td>
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<td>CYP2C19</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>207981, 01/01/2020</td>
<td>Tipiracil and Trifluridine (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
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<td>Indications and Usage, Clinical Studies</td>
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CLINICAL PHARMACOLOGY

Metabolism and Genetic Polymorphism

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. 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 TPMT 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 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.

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.

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<td>G6PD</td>
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<td>CYP2D6</td>
<td>Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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**12.3 Pharmacokinetics**

Cardiac Electrophysiology

The effect of 2 mg BID and 4 mg BID of DETROL immediate release tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18–65 years. Study subjects (approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs)) completed sequential 4-day periods of dosing with moxifloxacin 400 mg OD, tolterodine 2 mg BID, tolterodine 4 mg BID, and placebo. The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon coadministration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers [see DRUG INTERACTIONS (7.2)]. QT interval was measured over a 12-hour period following dosing, including the time of peak plasma concentration (Tmax) of tolterodine and at steady state (Day 4 of dosing). (…) Tolterodine’s effect on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QTc interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study. (…)

**12.2 Pharmacodynamics**

Cardiac Electrophysiology

The effect of 2 mg BID and 4 mg BID of DETROL immediate release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18–65 years. Study subjects (approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs)) completed sequential 4-day periods of dosing with moxifloxacin 400 mg OD, tolterodine 2 mg BID, tolterodine 4 mg BID, and placebo. The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon coadministration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers [see DRUG INTERACTIONS (7.2)]. QT interval was measured over a 12-hour period following dosing, including the time of peak plasma concentration (Tmax) of tolterodine and at steady state (Day 4 of dosing). (…) Tolterodine’s effect on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QTc interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study. (…)

**7.1 Potent CYP2D6 Inhibitors**

Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 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 [see CLINICAL PHARMACOLOGY (12.1)]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [see CLINICAL PHARMACOLOGY (12.3)].

**7.2 Potent CYP3A4 Inhibitors**

Ketoconazole (200 mg daily), a potent CYP3A4 inhibitor, increased the mean Cmax and AUC of tolterodine by 2- and 2.5-fold, respectively, in CYP2D6 poor metabolizers. For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, clarithromycin, or ritonavir, the recommended dose of DETROL LA is 2 mg once daily [see DOSAGE AND ADMINISTRATION(2.2) and CLINICAL PHARMACOLOGY (12.3)].

**5 WARNINGS AND PRECAUTIONS**

5.9 Use in Patients with Congenital or Acquired QT Prolongation

In a study of the effect of tolterodine immediate release tablets on the QT interval [see CLINICAL PHARMACOLOGY (12.2)], the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. (…)

**7 DRUG INTERACTIONS**

7.1 Potent CYP2D6 Inhibitors

Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 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 [see CLINICAL PHARMACOLOGY (12.1)]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [see CLINICAL PHARMACOLOGY (12.3)].

**7.2 Potent CYP3A4 Inhibitors**

Ketoconazole (200 mg daily), a potent CYP3A4 inhibitor, increased the mean Cmax and AUC of tolterodine by 2- and 2.5-fold, respectively, in CYP2D6 poor metabolizers. For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, clarithromycin, or ritonavir, the recommended dose of DETROL LA is 2 mg once daily [see DOSAGE AND ADMINISTRATION(2.2) and CLINICAL PHARMACOLOGY (12.3)].

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<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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. (…)</td>
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<tr>
<td>020281, 04/08/2019</td>
<td>Tramadol</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Boxed Warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Patient Counseling Information</td>
<td>BOXED WARNING 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 tponsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). ULTRAM 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 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 (see WARNINGS).</td>
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<td>Trametinib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>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 their breastfed 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)]. † ...</td>
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- 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](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.

### 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 = 38) and previously treated (N = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, non-randomized, open-label trial [Study BRF113928].

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

The safety of MEKINIST when administered with dabrafenib was evaluated in 93 patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019).

### 12 CLINICAL PHARMACOLOGY

#### 12.2 Pharmacodynamics

Administration of 1 mg and 2 mg MEKINIST to patients with BRAF V600 mutation-positive melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis).

#### 12.3 Pharmacokinetics

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-negative, unresectable or metastatic melanoma. (…)

(…)

(…)

(…)

(…)

(…)

(…)

(…)

(…)

(…)

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; NCT01859468). The COMBI-d study compared dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment 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 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 MIc 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; NCT02038947). (…)

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<td>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 97% also had extracranial metastases. (…) 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 THxID™-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 intranodal 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 (IIia, IIib, or IIIC). (…) 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 90), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIa (18%), Stage IIB (41%), Stage III (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 2.6 years. (See Table 13) (…) 14.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC) 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 Oncormine™ 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.</td>
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<th>G6PD</th>
<th>6 ADVERSE REACTIONS</th>
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<td>6.1 Clinical Trials Experience</td>
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<td>MEKINIST with Dabrafenib (…) The trial 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 RV 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>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>
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<td>1.1 Adjuvant Breast Cancer</td>
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<td>Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR positive or negative with one high risk feature [see Clinical Studies (14.1)]) breast cancer</td>
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<td>• as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel</td>
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<td>• with docetaxel and carboplatin</td>
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<td>• as a single agent following multi-modality anthracycline based therapy.</td>
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<td>1.2 Metastatic Breast Cancer</td>
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<td>Herceptin is indicated:</td>
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<td>• In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer</td>
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<td>• As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease</td>
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<td>1.3 Metastatic Gastric Cancer</td>
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**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](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. The results are shown in Table 10. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups. (See Table 10) (…)

**14.2 Metastatic Breast Cancer**

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

**Previously Untreated Metastatic Breast Cancer (Study 5)**

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). (…)

(…) Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (See Table 12) (…)

**Previously Treated Metastatic Breast Cancer (Study 6)**

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. (…)

**14.3 Metastatic Gastric Cancer**

The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1.

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<td>016792, 11/29/2018</td>
<td>Trastuzumab (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
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<tr>
<td>07/01/2008</td>
<td>020438, 07/01/2008</td>
<td>Tretinoin</td>
<td>Oncology</td>
<td>PML-RARA</td>
<td>Indications, Usage, Warnings, Clinical Pharmacology</td>
<td>…</td>
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<tr>
<td>06/30/2020</td>
<td>103792</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>…</td>
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<tr>
<td>11/29/2018</td>
<td>213687, 06/30/2020</td>
<td>Trimipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>…</td>
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<tr>
<td>01/17/2014</td>
<td>016792, 07/17/2014</td>
<td>Tucatinib</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>…</td>
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<td>04/17/2020</td>
<td>213411</td>
<td>Tucatinib</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>…</td>
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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
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<tbody>
<tr>
<td>205382, 06/06/2019</td>
<td>Umeclidinium</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>HER2CLIMB (…) The safety of TUKYSA in combination with trastuzumab and capcitabine was evaluated in HER2CLIMB [see Clinical Studies (14)]. Patients received either TUKYSA 200 mg twice daily plus trastuzumab and capcitabine (n=404) or placebo plus trastuzumab and capcitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. (…)</td>
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<tr>
<td>211675, 08/16/2019</td>
<td>Upadacitinib</td>
<td>Rheumatology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Upadacitinib and Cytochrome P450 2D6: In vitro metabolism of upadacitinib is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to upadacitinib (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).</td>
</tr>
<tr>
<td>761044, 09/23/2016</td>
<td>Ustekinumab</td>
<td>Dermatology and Gastroenterology</td>
<td>IL12A, IL12B, IL23A</td>
<td>Warnings and Precautions</td>
<td>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), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (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.</td>
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<tr>
<td>209241, 08/10/2018</td>
<td>Valbenazine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.3 Dosage Recommendations for Known CYP2D6 Poor Metabolizers Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].</td>
</tr>
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<tr>
<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>
<td>BOXED WARNING: WARNING: LIFE THREATENING ADVERSE REACTIONS Patients with Mitochondrial Disease There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase y (POLG) gene (e.g., Alpers-Huttenlocher Syndrome). Depakene is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder [see Contraindications (4)]. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice [see Warnings and Precautions (5.1)].</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>
<td>4 CONTRAINdications (…) Depakene is contraindicated in patients known to have urea cycle disorders [see Warnings and Precautions (5.6)].</td>
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<td>202429, 05/18/2020</td>
<td>Vemurafenib (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, Patient Counseling Information</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
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<td>1.1 Unresectable or Metastatic Melanoma</td>
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<td>ZELBORAF® is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.</td>
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<td>Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].</td>
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<td>1.2 Erdheim-Chester Disease</td>
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<td>ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.</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>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 <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>5.2 Tumor Promotion in BRAF Wild-Type Melanoma</td>
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<td>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)].</td>
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<td>5.5 QT Prolongation</td>
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<td>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)].</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>(…) Unresectable or Metastatic Melanoma with BRAF V600E Mutation</td>
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<td>This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 [see Clinical Studies (14)].</td>
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<td>Erdheim-Chester Disease (ECD)</td>
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<td>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.</td>
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<td>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.</td>
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<td>In Trial 4, the most commonly reported adverse reactions (&gt; 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.</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 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.</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics</td>
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<td>Cardiac Electrophysiology</td>
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<td>In a multi-center, open-label, single-arm study in 132 patients with BRAF V600E mutation-positive metastatic melanoma, patients administered vemurafenib 960 mg orally twice daily did not experience large changes in mean QTc interval (i.e., &gt; 20 ms) from baseline.</td>
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<td>12.3 Pharmacokinetics</td>
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<td>The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of 960 mg twice daily with dosing approximately 12 hours apart. The population pharmacokinetic analysis pooled data from 458 patients. At steady-state, vemurafenib exhibits linear pharmacokinetics within the 240 mg to 960 mg dose range.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>Treatment-Naïve Patients with BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma</td>
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<td>Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naïve, BRAF V600E mutation-positive unresectable or metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, to receive ZELBORAF 960 mg by mouth twice daily (n=337) or dacarbazine 1000 mg/m² intravenously on Day 1 every 3 weeks (n=338). (See Table 5).</td>
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<td>Patients with BRAF V600E Mutation-Positive Metastatic Melanoma Who Received Prior Systemic Therapy (…) In a single-arm, multicenter, multinational trial (Trial 2), 132 patients with BRAF V600E mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, who had received at least one prior systemic therapy, received ZELBORAF 960 mg by mouth twice daily. (…)</td>
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<th>Labeling Text‡</th>
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<tbody>
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<td>202429, 05/18/2020</td>
<td>Venetoclax (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>Patients with BRAF V600E Mutation-Positive Melanoma with Brain Metastases</td>
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<td>The activity of ZELBORAF for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in an open-label, multicenter, single-arm, two cohort trial (Trial 3) (See Table 6, ‡)</td>
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<td>Patients with Wild-Type BRAF Melanoma</td>
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<td></td>
<td>ZELBORAF has not been studied in patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].</td>
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<td>Patients with Erdheim-Chester Disease (ECD)</td>
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<td>An open-label, multicenter, single-arm, multiple cohort study of ZELBORAF (Trial 4) was conducted in patients ≥ 16 years of age with non-melanoma BRAF V600E mutation-positive diseases. (…)</td>
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<td>17 PATIENT COUNSELING INFORMATION</td>
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<td>Healthcare providers should advise patients of the potential benefits and risks of ZELBORAF and instruct their patients to read the Medication Guide before starting ZELBORAF therapy. Inform patients of the following:</td>
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<td>• Evidence of BRAF V600E mutation in the tumor specimen with an FDA approved test is necessary to identify patients for whom treatment with ZELBORAF is indicated [see Dosage and Administration (2.1)]. (…)</td>
</tr>
<tr>
<td>020699, 12/19/2017</td>
<td>Venlafaxine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
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<td>7.5 Weight Loss Agents</td>
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<td>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)</td>
</tr>
<tr>
<td>208573, 05/29/2020</td>
<td>Venetoclax (1)</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy</td>
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<td>CLL (1)</td>
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<td>A total of 432 patients were randomized, 216 to each study arm. Baseline demographic and disease characteristics were similar between the study arms. (…)</td>
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<td>The median age was 72 years (range: 41 to 89 years), 89% were white, 67% 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 CIROC score was 8.5 (range: 0 to 28) and 58% of patients had Clcr &lt;70 mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 10%, 11q deletion in 19%, and unmutated IgVH in 57%. (…)</td>
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<td>MURANO</td>
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<td>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) (…)</td>
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<td>Monotherapy</td>
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<td>The efficacy of VENCLEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies. Study M13-982</td>
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<td>Chromosome 17q</td>
<td>Clinical Studies</td>
<td>The efficacy of VENCLEXTA was established in study M13-982 (NCT01889186), an openlabel, 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 Vyssis 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 ≥5 cm, 30% of patients had ALC ≥25 x 10^9/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: 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 ≥5 cm, 31% had an absolute lymphocyte count ≥25 x 10^9/L, 57% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)</td>
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<td>208573, 05/29/2020</td>
<td>Venetoclax (3)</td>
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<td>TP53</td>
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<td>14 CLINICAL STUDIES 14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy COL 14 (…) 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%. (…)</td>
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<td>14 CLINICAL STUDIES 14.2 Acute Myeloid Leukemia Study M14-358 VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02303773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML 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 (…) 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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| 208573, 05/29/2020                      | Venetoclax (6) | Oncology | IGH | Clinical Studies | 14 CLINICAL STUDIES 14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy  
CCL14  
(...)

| 208573, 05/29/2020                      | Venetoclax (7) | Oncology | NPM1 | Clinical Studies | 14 CLINICAL STUDIES 14.2 Acute Myeloid Leukemia  
Study M14-358  
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) (...)

| 208573, 05/29/2020                      | Venetoclax (8) | Oncology | FLT3 | Clinical Studies | 14 CLINICAL STUDIES 14.2 Acute Myeloid Leukemia  
Study M14-358  
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) (...)

| 212154, 08/12/2020                     | Viltolarsen | Neurology | DMD | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
VILT须POSOU 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 VILT须POSOU [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 VILT须POSOU, 32 patients have been exposed to VILT须POSOU 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. (...)

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| 202497, 06/08/2020                     | 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. |

| 021266, 04/30/2019                     | 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, CYP2C19, CYP2C9 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 (AUCτ) 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 (AUCτ) 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)]. |

| 204447, 10/19/2018                    | 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)]. |

| 213137, 11/25/2019                    | Voxelotor    | Hematology   | HBB     | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY
  12.3 Pharmacokinetics
  Metabolism and Elimination
  Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carbonyl acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers. (…)

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| 009218, 08/14/2017                     | Warfarin (1) | Hematology | CYP2C9 | Dosage and Administration, Drug Interactions, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.3 Initial and Maintenance Dosing
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)]

2.5 Pharmacogenomics
CYP2C9 and VKORC1 Polymorphisms
- The S-enantiomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9, and *11 alleles in Caucasians. Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle through inhibition of VKOR, a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (e.g., −1639G>A) have been associated with variable warfarin dose requirements. VKORC1 and CYP2C9 genotype information, when available, can assist in selection of the initial dose of warfarin [see Dosage and Administration (2.3)].

2.3 Pharmacokinetics
Metabolism
The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic cytochrome P-450 (CYP450) microsomal enzymes to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols) with minimal anticoagulant activity. Identified metabolites of warfarin include dehydrowarfarin, two diastereomeric alcohols, and 4′-hydroxywarfarin. The CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the in vivo anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance [see Clinical Pharmacology (12.5)].

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