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 of Pharmacogenomic Biomarkers in Drug Labeling**

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<table>
<thead>
<tr>
<th>NDA/ANDA/BLA 020977, 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>
| 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
Hyper-sensitivity 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.
• A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

1 INDICATIONS AND USAGE
VERZENIO® (abemaciclib) is indicated:

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</table>
| 208716, 03/30/2020                      | Abemaciclib (2) | Oncology | ERBB2 (HER2) | Reactions, Clinical Studies | • 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 with disease progression following endocrine therapy.  
• as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. |

### 6 ADVERSE REACTIONS

**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**

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

**MONARCH 2: VERZENIO in Combination with Fulvestrant**

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

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

**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 (NCT02102960) 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:

• 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

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.

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<td>125427, 05/03/2019</td>
<td>Ado-Trastuzumab Emtansine</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>1 INDICATIONS AND USAGE</td>
<td>KADCYLA®, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy.</td>
</tr>
</tbody>
</table>

1.1 Metastatic Breast Cancer (MBC) | KADCYLA®, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy. |

1.2 Early Breast Cancer (EBC) | KADCYLA®, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA [see Dosage and Administration (2.1)]. |

2.1 Patient Selection | Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1)], Clinical Studies (14)]. Assessment of HER2 protein overexpression and/or HER2 gene amplification should be performed using FDA-approved tests specific for breast cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics. Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. |

6 ADVERSE REACTIONS | 6.1 Clinical Trials Experience | Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the WARNINGS AND PRECAUTIONS reflect exposure to KADCYLA as a single agent at 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) in 1624 patients including 884 patients with HER2-positive metastatic breast cancer and 740 patients with HER2-positive early breast cancer (KATHERINE trial). | Metastatic Breast Cancer | In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. The most common (≥ 25%) adverse reactions were fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation and epistaxis. |

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The adverse reactions described in Table 3 were identified in patients with HER2-positive metastatic breast cancer treated in the EMIILA trial [see Clinical Studies (14.1)]. Patients were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.9 months and 5.3 months for patients treated with lapatinib and capecitabine, respectively. (…) Early Breast Cancer

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

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

12.3 Pharmacokinetics
Effect of Hepatic Impairment
The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=15), mild (Child-Pugh A; n=10) and moderate (ChildPugh B; n=9) hepatic impairment. (…)

14 CLINICAL STUDIES
14.1 Metastatic Breast Cancer
The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial (EMILIA) (NCT00829166) of 991 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only prior adjuvant therapy were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. (…) 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 radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory using Ventana’s PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. Randomization was stratified by HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent(s)), and pathological nodal status evaluation after preoperative therapy. KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. (…)

The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 94% of these patients received pertuzumab. (…)

201290,
10/11/2019
Afatinib Oncology EGFR
1 INDICATIONS AND USAGE
1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer
GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see Clinical Pharmacology (12.1) and Clinical Studies (14.1)]. Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations [see Clinical Studies (14.1)].

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC

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<td></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>2.1 Patient Selection for Non-Resistant EGFR Mutation-Positive Metastatic NSCLC. Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of nonresistant EGFR mutations in tumor specimens [see Indications and Usage (1.1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at [<a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>].</td>
</tr>
</tbody>
</table>

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The data described below reflect exposure to GILOTRIF as a single agent in LUX-Lung 3, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in LUX-Lung 8, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy. (…)

EGFR Mutation-Positive, Metastatic NSCLC

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). (…)

14 CLINICAL STUDIES

14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer

The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical 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 RQG 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 ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while 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 afatinib 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 afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit. • LUX-Lung 6 was a randomized, multicenter study comparing treatment with afatinib 40 mg to intravenous gemcitabine 1000 mg/m2 on day 1 and day 8 plus cisplatin 75 mg/m2 on day 1 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit.

Among the 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), 66% 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, and 6% were current smokers. Baseline disease characteristics were 57% 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.

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<td>Inborn Errors of Metabolism</td>
<td>GAA</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td></td>
<td></td>
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<td></td>
<td>5.2 Immune-Mediated Reactions</td>
</tr>
</tbody>
</table>
|                                        |      |                 |           |                  | Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrotizing skin lesions [see Adverse Reactions (6.3)]. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alglucosidase alfa. These reactions occurred 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 alglucosidase alfa should undergo periodic urinalysis [see Adverse Reactions (6.3)]. (…)
|                                        |      |                 |           |                  | 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 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 a better 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 to rhGAA may experience reduced clinical alglucosidase alfa treatment efficacy, such as loss of motor function, ventilator dependence, or death. |
| 12/16/2020, 02/26/2018                 | Allopurinol | Oncology | HLA-B | WARNINGS | WARNINGS: DISCONTINUE ALOPRIM AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE A HYPERSENSITIVITY REACTION. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking allopurinol. These reactions occur in approximately 5 in 10,000 (0.05%) patients taking allopurinol. Other serious hypersensitivity reactions that have been reported include exfoliative, urticarial and purpuric lesions; generalized vasculitis; and irreversible hepatotoxicity. The HLA-B*58:01 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol. Patients who carry the HLA-B*58:01 allele are at a higher risk of allopurinol hypersensitivity syndrome (AHS), but hypersensitivity reactions have been reported in patients who do not carry this allele. The frequency of this allele is higher in individuals of African, Asian (e.g., Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry. Prior to starting ALOPRIM, consider testing for the HLA-B*58:01 allele in genetically at-risk populations. The use of ALOPRIM is not recommended in HLA-B*58:01 positive patients unless the benefits clearly outweigh the risks. |

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**Table of Pharmacogenomic Biomarkers in Drug Labeling**

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<th>Therapeutic Area</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</table>
| 212526, 09/01/2020                    | Alpelisib (1) | Oncology | ERBB2 (HER2) | 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. |
| 212526, 09/01/2020                    | Alpelisib (2) | Oncology | ESR (Hormone Receptor) | 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. |
| 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. |

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</table>
| 209321, 05/06/2019                     | Amifampridine | Neurology        | NAT2        | Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology | 6 ADVERSE REACTIONS
6.1 Clinical Trial Experience

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

14 CLINICAL STUDIES

SOLAR-1 (NCT02437319) was a randomized, double-blind, placebo-controlled trial of PIKRAY 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 aromastase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s). Overall, 60% of enrolled patients had tumors with one or more PIK3CA mutations in tissue, 50% had liver/lung metastases, and 6% had previously been treated with a CDK4/6 inhibitor.

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

Efficacy results for the cohort with a PIK3CA mutation in tumor tissue are presented in Table 8 and Figure 1. PFS results for the cohort with a PIK3CA mutation by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. Consistent results were seen in patients with tissue or plasma PIK3CA mutations. At the time of final PFS analysis, 27% (92/341) of patients had died, and overall survival follow-up was immature.

No PFS benefit was observed in patients whose tumors did not have a PIK3CA tissue mutation (HR = 0.85; 95% CI: 0.58, 1.25). (See Table 8 and Figure 1)

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| 208078, 11/28/2018                      | Amifampridine Phosphate | Neurology | NAT2 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSEAGE AND ADMINISTRATION
2.4 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers
The recommended starting dosage of FIRDAPSE in known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily, taken orally in 3 divided doses [see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3, 12.5)].

8 USE IN SPECIFIC POPULATIONS
8.8 NAT2 Poor Metabolizers
Exposure of FIRDAPSE is increased in patients who are N-acetyltransferase 2 (NAT2) poor metabolizers [see Clinical Pharmacology (12.5)]. Therefore, initiate FIRDAPSE in patients who are known NAT2 poor metabolizers at the lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions [see Dosage and Administration (2.4)]. Consider dosage modification of FIRDAPSE for patients who are known NAT2 poor metabolizers as needed based on clinical effect and tolerability.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
The effect of FIRDAPSE on QTc interval prolongation was studied in a double blind, randomized, placebo and positive controlled study in 52 healthy individuals who are slow acetylators. At an exposure 2-fold the expected maximum therapeutic exposure of amifampridine, FIRDAPSE did not prolong QTc to any clinically relevant extent.

12.5 Pharmacogenomics
Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of FIRDAPSE metabolism. Poor metabolizers, also referred to as "slow acetylators" (i.e., carriers of two reduced function alleles), have 3.5- to 4.5-fold higher Cmax, and 5.6- to 9-fold higher AUC than normal metabolizers, also referred to as "fast/rapid acetylators" (i.e., carriers of two normal function alleles). Therefore, FIRDAPSE should be initiated at the lowest recommended starting dosage (15 mg/day) in known NAT2 poor metabolizers, and such patients should be closely monitored for adverse reactions [see Dosage and Administration (2.4) and Use in Specific Populations (8.8)].

In the general population, the NAT2 poor metabolizer phenotype prevalence is 40–60% in the White and African American populations, and in 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent). |
| 085971, 07/17/2014                      | Amitriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS
Drugs Metabolized by P450 2D6
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher 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. (…)

| 05/21/2021, 761219                     | Amivantamab-vmjjw | Oncology | EGFR | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
Ryrevant is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)], whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSEAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for treatment with RYREVANT based on the presence of EGFR exon 20 insertion mutations [see Clinical Studies (14.1)]. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
The data described below reflect exposure to RYREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year. (See Tables 6 and 7) (…)

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics

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<td>07/2691, 07/17/2014</td>
<td>Amoxapine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td><strong>PRECAUTIONS</strong> 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 &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA) In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. (…)</td>
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<tr>
<td>204325, 09/15/2017</td>
<td>Amphetamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>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 norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-alpha-hydroxy-ephemintamine 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.</td>
<td></td>
</tr>
<tr>
<td>103950, 12/18/2020</td>
<td>Anakinra</td>
<td>Rheumatology</td>
<td>NLRP3</td>
<td>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 8 mg/kg daily to control active inflammation. Adjust doses in 0.5 to 1 mg/kg increments. Once daily administration is generally recommended, but the dose may be split into twice daily administrations. Each syringe is intended for a single use. A new syringe must be used for each dose. Any unused portion after each dose should be discarded. 5 WARNINGS AND PRECAUTIONS 5.1 Serious Infections KINERET has been associated with an increased incidence of serious infections (2%) vs. Placebo (0.1%) in clinical trials in RA. Administration of KINERET in RA should be discontinued if a patient develops a serious infection. In KINERET treated NOMID and DIRA patients the risk of a disease flare when discontinuing KINERET treatment should be weighed against the potential risk of continued treatment. Treatment with KINERET should not be initiated in patients with active infections. The safety and efficacy of KINERET in immunosuppressed patients or in patients with chronic infections have not been evaluated. (…) 5.6 Neutrophil Count Patients receiving KINERET may experience a decrease in neutrophil counts. Neutrophil counts should therefore be assessed prior to initiating KINERET treatment, and while receiving KINERET, monthly for 3 months, and thereafter quarterly for a period up to 1 year. In the placebo-controlled studies, 8% of RA patients receiving KINERET had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Nine KINERET-treated patients (0.4%) experienced neutropenia (ANC &lt; 1 x 10^9/L). This is discussed in more detail in the Adverse Reactions (6) Hematologic Events section. In 43 NOMID patients followed up for at least 6 months 2 patients experienced neutropenia that resolved over time continued KINERET treatment. (see Adverse Reactions (6.1))</td>
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<td>020541, 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></td>
</tr>
</tbody>
</table>

6 ADVERSE REACTIONS
6.2 Clinical Study Experience in NOMID
The data described herein reflect an open-label study in 43 NOMID patients exposed to KINERET for up to 60 months adding up to a total exposure of 159.8 patient years. Patients were treated with a starting dose of 1 to 2 mg/kg/day and an average maintenance dose of 3.4 mg/kg/day adjusted depending on the severity of disease. Among pediatric NOMID patients, doses up to 7.6 mg/kg/day have been maintained for up to 15 months. (…) Immunogenicity
The immunogenicity of KINERET in NOMID patients was not evaluated.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available data from retrospective studies and case reports on KINERET use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. There are risks to the mother and fetus associated with active rheumatoid arthritis or Cryopyrin-Associated Periodic Syndromes (CAPS). In animal reproduction studies, subcutaneous administration of anakinra to pregnant rats and rabbits during organogenesis demonstrated no evidence of fetal harm at doses up to 25 times the maximum recommended human dose (MRHD). (…) Clinical Considerations Disease-associated maternal and/or embryo/fetal risk Published data suggest the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or CAPS is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (<2500 grams), and small for gestational age at birth.

8.4 Pediatric Use
Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
The NOMID study included 36 pediatric patients: 13 below 2 years, 18 between 2 and 11 years, and 5 between 12 and 17 years of age. A subcutaneous KINERET starting dose of 1–2 mg/kg/day was administered in all age groups. An average maintenance dose of 3–4 mg/kg/day was adequate to maintain clinical response throughout the study irrespective of age but a higher dose was, on occasion, required in severely affected patients. The prefilled syringe does not allow doses lower than 20 mg to be administered.

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
(…) In NOMID patients, at a median SC dose of 3 mg/kg once daily and a median treatment time of 3.5 years, the median (range) steady-state serum exposure of anakinra was Cmax 3628 (655–8511) ng/mL (n=16) and C24h 203 (53–1979) ng/mL (n=16). The median (range) half-life of anakinra was 5.7 (3.1–28.2) hours (n=12). There was no obvious gender difference. (…) Clinical Studies
14.2 Clinical Studies in NOMID
The efficacy of KINERET was evaluated in a prospective, long-term, open-label and uncontrolled study which incorporated a withdrawal period in a subset of 11 patients. This study included 43 NOMID patients 0.7 to 46 years of age treated for up to 60 months. Patients were given an initial KINERET dose of 1–2.4 mg/kg body weight. During the study, the dose was adjusted by 0.5 to 1 mg/kg increments to a protocol-specified maximum of 10 mg/kg daily, titrated to control signs and symptoms of disease. The maximum dose actually studied was 7.6 mg/kg/day. The average maintenance dose was 3 to 4 mg/kg daily. In general, the dose was given once daily, but for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, oral ulcers, and headache. In addition, serum amyloid A (SAA), hsCRP, and ESR levels were monitored. Changes in clinical and laboratory parameters from baseline to Months 3 to 6 and from Month 3 (before withdrawal) to the end of the withdrawal period were assessed in the subset of patients who underwent withdrawal. The estimated changes from baseline in DSSS are summarized through Month 60 in Table 6. Results were consistent across all subgroups, including age, gender, presence of CIAS1 mutation, and disease phenotype. Improvements occurred in all individual disease symptoms comprising the DSSS (Table 7), as well as in the serum markers of inflammation. For the 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of KINERET therapy. Upon withdrawal of treatment, the median time until disease flare criteria were met was 5 days. (See Tables 6 and 7). KINERET treatment also appeared to be associated with improvement of, or stability in, assessments of other NOMID disease manifestations, such as CNS, audiogram, and visual acuity data, up to Month 60.

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<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology 12.5 Pharmacogenomics Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Demethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.</td>
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<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology 12.5 Pharmacogenomics Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Demethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.</td>
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<td>024346, 02/23/2017</td>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology 2.7 Dosage Adjustments for Cytochrome P450 Considerations Dosage adjustments are recommended for patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response. (See Table 2)</td>
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<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</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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| 021248, 11/30/2018                     | Arsenic Trioxide | Oncology | PML-RARA | * Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.

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<td>022466, 11/02/2018</td>
<td>Articaine and Epinephrine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS  5.4 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>022466, 11/02/2018</td>
<td>Articaine and Epinephrine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS  5.4 Methemoglobinemia  Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>761034, 12/26/2020</td>
<td>Atezolizumab (1)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>5.4 Increased Mortality in Patients with Metastatic TNBC when TECENTRIQ is Used with Paclitaxel  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 unselectable locally advanced or metastatic urothelial carcinoma or triple-negative breast cancer have not been demonstrated [see Indications and Usage (1.3) and Clinical Studies (14.4)]. Do not substitute paclitaxel protein-bound with paclitaxel in clinical practice for metastatic TNBC outside of controlled trials. (…)</td>
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<tr>
<td>6.2 Immunogenicity</td>
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</table>
| (…) Among 434 patients with 
  TNBC 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 TNBC in IMpassion130, 12% 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 (21–86 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 EOCG status had no clinically significant effect 
  on the systemic exposure of atezolizumab. (…) |
| 14 CLINICAL STUDIES                  |      |                  |            |                  |                |
| 14.1 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 67 years, 81% were male, 
  19% female, and 88% were White. Twenty-eight percent 
  of patients had non-bladder urothelial carcinoma and 
  56% had visceral metastases. Seventy-two percent 
  of patients had an ECOG PS of 0 or 1. Reasons 
  for ineligibility for cisplatin-containing chemotherapy 
  were: 66% had impaired renal function, 28% had an 
  ECOG PS of 2, 16% had a hearing loss ≥ 25 dB, and 9% 
  had Grades 2-4 peripheral neuropathy at baseline. Thirty-one percent 
  of patients had disease progression following prior platinum-containing 
  neoadjuvant or 
  adjuvant chemotherapy. 
  Confirmed ORR in all patients and the 
  two PD-L1 subgroups are summarized in Table 22. The median follow-up 
  time for this study was 14.4 months. In 24 
  patients with disease progression following 
  neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%). (See Table 22) (…) |
| (…) Both cisplatin-eligible and 
  cisplatin-ineligible patients are included in the study. Tumor specimens 
  were evaluated prospectively using the VENTANA PD-L1 
  (SP142) Assay at a central laboratory. The Independent Data Monitoring 
  Committee (IDMC) for the study conducted a review of 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) (…) |
| 14.2 Non-Small Cell Lung Cancer       |      |                  |            |                  |                |
| (…) Tumor samples 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 in all patients and the two PD-L1 subgroups are summarized in Table 22. 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) (…) |

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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 tumorinfiltrating 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.

Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous) and PD-L1 expression (TC ≥ 1% and any IC vs. TC < 1% and IC ≥ 1%). Patients were randomized (1:1) to receive one of the following treatment arms:

- **Arm A: TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity**
- **Arm B: Platinum-based chemotherapy**

The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥50% or IC ≥10%; TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%. Among the 205 chemotherapy-naïve patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) excluding those with EGFR or ALK genomic tumor aberrations, the median age was 65.0 years (range: 33 to 87), and 70% of patients were male. The majority of patients were White (82%) and...
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**Asian (17%), Baseline ECOG performance status was 0 (36%) or 1 (64%); 88% were current or previous smokers; and 76% of patients had non-squamous disease while 24% of patients had squamous disease.**

The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥50% or IC ≥10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥25% or IC ≥5%; and TC ≥0% or IC ≥5%) at the interim or final analyses. Efficacy results for patients with NSCLC with high PD-L1 expression are presented in Table 24 and Figure 1. (See Table 24 and Figure 1)

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<td>Atezolizumab (2)</td>
<td>Oncology</td>
<td>Gene Signature (T-effector)</td>
<td>Clinical Studies</td>
<td></td>
</tr>
</tbody>
</table>

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 metastatic 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) of the primary tumor. The randomization was performed using a computer-generated randomization list. Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) of the primary tumor. The randomization was performed using a computer-generated randomization list. 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.

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

(…) Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) of the primary tumor. The randomization was performed using a computer-generated randomization list. Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) of the primary tumor. The randomization was performed using a computer-generated randomization list. 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.

14.5 Clinical Studies

<table>
<thead>
<tr>
<th>14.2 Non-Small Cell Lung Cancer</th>
<th>Metastatic Chemotherapy-Naive Non-Squamous NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMpower150</td>
<td>IMpower150 had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 status.</td>
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| 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. |
|                                         | 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.  
- 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.  
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14 CLINICAL STUDIES
14.2 Non-Small Cell Lung Cancer

14.2 Non-Small Cell Lung Cancer Metastatic Chemotherapy-Naive NSCLC with High PD-L1 Expression

The efficacy of TECENTRIQ was evaluated in IMpower110 (NCT02409342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC who had tumors expressing PD-L1 (PD-L1 stained ≥ 1% of tumor cells (TC) ≥ 1%) or PD-L1 stained ≥ 1% of tumor cells (TC ≥ 1%) who 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 I C ≥ 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 immunomodulatory 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 ≥ 25% or IC ≥ 5%; and TC ≥ 1% or IC ≥ 1%. Among the 205 chemotherapy-naive patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or I C ≥ 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 76% of patients had non-squamous disease while 24% of patients had squamous disease. (See Table 24 and Figure 1) (…)
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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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5 WARNINGS AND PRECAUTIONS

5.2 Laboratory Tests

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

5.13 Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients who are known to be CYP2D6 PMs

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Child and Adolescent Clinical Trials

(….) The following adverse reactions occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: insomnia (11% of PMs, 6% of EMs); weight decreased (7% of PMs, 4% of EMs); constipation (7% of PMs, 4% of EMs; depression (7% of PMs, 4% of EMs); tremor (5% of PMs, 1% of EMs); excitation (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). (…)

Adult Clinical Trials

(…) 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 metaboliser (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 (6% 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). (…)

7 DRUG INTERACTIONS

7.2 Effect of CYP2D6 Inhibitors on Atomoxetine

In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and Cox, max is about 3- to 4-fold greater than atomoxetine alone.

In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Insufficiency

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

8.7 Renal Insufficiency

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

8.9 Ethnic Origin

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

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of STRATTERA on QTc prolongation was evaluated in a randomized, double-blinded, positive-(moxifloxacin 400 mg) and placebo-controlled, cross-over study in healthy male CYP2D6 poor metabolizers. A total of 120 healthy subjects were administered STRATTERA (20 mg and 60 mg) twice daily for 7 days. No large changes in QTc interval (i.e., increases >0 ms from baseline, absolute QTc >480 ms) were observed in the study. However, small changes in QTc interval cannot be excluded from the current study, because the study failed to demonstrate assay sensitivity. There was a slight increase in QTc interval with increased atomoxetine concentration.

12.3 Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 6 hours. A fraction of the population

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<td>(about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity (extensive metabolizers (EMs)) (...). Absorption and distribution Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (Cmax) are reached approximately 1 to 2 hours after dosing. (…) Metabolism and elimination Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Co-administration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (see Warnings and Precautions (5.13)). Atomoxetine did not inhibit or induce the CYP2D6 pathway. The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equivalent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs). Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours). (…)</td>
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<td></td>
<td>212608, 06/16/2021</td>
<td>Avapritinib (1)</td>
<td>Oncology</td>
<td>PDGFRA</td>
<td>1 INDICATIONS AND USAGE 1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST) AYVAKIT is indicated for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations [see Dosage and Administration (2.1)]. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection for GIST Harboring PDGFRA Exon 18 Mutations Select patients for treatment with AYVAKIT 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 Patients with unresectable or metastatic 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 &gt;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 6)</td>
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<tr>
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<td>212608, 06/16/2021</td>
<td>Avapritinib (2)</td>
<td>Oncology</td>
<td>KIT</td>
<td>14 CLINICAL STUDIES 14.2 Advanced Systemic Mastocytosis The efficacy of AYVAKIT was demonstrated in EXPLORER (NCT02561988) and PATHFINDER (NCT03580655), two multi-center, single-arm, open-label clinical trials. Response-evaluable patients include those with a confirmed diagnosis of AdvSM per World Health Organization (WHO) and deemed evaluable by modified international working group-myeloproliferative neoplasms research and treatmentEuropean competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline as adjudicated by an independent central committee, who received at least 1 dose of AYVAKIT, had at least 2 post-baseline bone marrow</td>
</tr>
</tbody>
</table>

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<td>210238, 06/30/2019</td>
<td>Avatrombopag (1)</td>
<td>Hematology</td>
<td>F2 (Prothrombin)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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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>PROC</td>
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<td>Avatrombopag (4)</td>
<td>Hematology</td>
<td>PROST</td>
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<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>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<em>2 and CYP2C9</em>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=49]).</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 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance status was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive (≥2).</td>
</tr>
</tbody>
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</thead>
</table>
| Azathioprine (1) | Rheumatology | TPMT | Dosage and Administration, Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology | **DOSAGE AND ADMINISTRATION**

**Patients with TPMT and/or NUDT15 Deficiency**

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

**Homozygous deficiency in either TPMT or NUDT15**

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

**Heterozygous deficiency in TPMT and/or NUDT15**

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

**WARNINGS**

Cytopenias

TPMT or NUDT15 Deficiency

(…)

**PRECAUTIONS**

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

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

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|-----------------|-----------------------|--------------|------------------|-----------|-------------------|-----------------|
| 016324, 12/20/18| NDA/ANDA/BLA          | Azathioprine (2) | Rheumatology     | NUDT15   | Dosage and Administration, Warnings, Precautions, Adverse Reactions, Clinical Pharmacology | ADVERSE REACTIONS

Hematologic

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

CLINICAL PHARMACOLOGY

(…) 6-MP undergoes two major inactivation routes. One is thiol methylation, which is catalyzed by the enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-6-MP (6-MeMP). Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) to form 6-thiouric acid. The nucleotide diphosphatase (NUDT15) enzyme is involved in conversion of the 6-TGNs to inactive 6-TG monophosphates. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities.

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. (…)

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

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

Because of the risk of increased toxicity, dosage reduction is recommended in patients known to have heterogeneous deficiency of TPMT or NUDT15. Patients with abnormal CBC results that do not respond to dose reduction (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). When patients are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests).

ADVERSE REACTIONS

Hematologic

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

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

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

WARNINGS

Cytopenias

TPMT or NUDT15 Deficiency

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

CLINICAL PHARMACOLOGY

(…) The nucleotide diphosphatase (NUDT15) enzyme is involved in conversion of the 6-TGNs to inactive 6-TG monophosphates. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities. Genetic polymorphisms influence TPMT and NUDT15 activity. Several published studies indicate that patients with reduced
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| 206256, 01/08/2020                     | Belinostat | Oncology | UGT1A1 | Dosage and Administration, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.3 Patients with Reduced UGT1A1 Activity
Reduce the starting dose of Beleodaq to 750 mg/m2 in patients known to be homozygous for the UGT1A1*28 allele [see Clinical Pharmacology (12.5)]. |

210498, 01/23/2019
Bisplatin (1) | Oncology | BRAF | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 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)]. |

TPMT or UDT15 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 UDT15 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 intermediate metabolizers). The TPMT-2, TPMT-3A, and TPMT-3C alleles account for about 95% of individuals with reduced levels of TPMT activity. UDT15 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 UDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of UDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function UDT15 alleles have been observed. (…)

2.2 Interstitial Lung Disease
In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 2 patients (0.3%) developed interstitial lung disease (ILD). (…)

3.6 Ocular Toxicity
Retinal Vein Occlusion
RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with encorafenib in patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 2 patients (0.3%) developed interstitial lung disease (ILD), including pneumonitis. (…)

4.6 Rhabdomyolysis
Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevation of laboratory values of serum CPK occurred in 5% of patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), rhabdomyolysis was reported in 1 patient (0.1%). (…)

6.1 Clinical Trials Experience
(…)

6.2 Safety Testing
The safety and efficacy of MEKTOVI in patients with BRAF mutation-positive melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)].

- Patients with 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.
- Patients with TPMT or UDT15 deficiency require alternative therapy or dose modification.
- 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 intermediate metabolizers).
- The TPMT-2, TPMT-3A, and TPMT-3C alleles account for about 95% of individuals with reduced levels of TPMT activity.
- UDT15 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 UDT15 gene, and approximately 21% have one loss-of-function allele.
- The p.R139C variant of UDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function UDT15 alleles have been observed.

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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>
<tbody>
<tr>
<td>210498, 01/23/2019</td>
<td>Binimetinib (2)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Drug Interaction Studies Clinical Studies Effect of UGT1A1 inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Simulations predict similar Cmax of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).</td>
</tr>
<tr>
<td>125557, 03/11/2021</td>
<td>Binumatomab (1)</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL The safety data described below reflect exposure to BLINCYTO in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO (n = 267) or standard of care (SOC) chemotherapy (n = 109).</td>
</tr>
<tr>
<td>125557, 03/11/2021</td>
<td>Binumatomab (2)</td>
<td>Oncology</td>
<td>CD19</td>
<td>Indications and Usage</td>
<td>1 INDICATIONS AND USAGE 1.1 MRD-positive B-cell Precursor ALL BLINCYTO is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children. This indication is approved based on accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. 1.2 Relapsed/Refractory B-cell Precursor ALL BLINCYTO is indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.</td>
</tr>
<tr>
<td>202258, 01/30/2017</td>
<td>Boceprevir</td>
<td>Infectious Diseases</td>
<td>IFN13 (IL28B)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics 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 653 of 1048 (62%) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPONSE-2 (previous partial responders and relapsers). Among subjects that received at least one dose of placebo or VICTREXIS (Modified-Intent-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 VICTREXIS. 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>
</tbody>
</table>

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</table>
| 203341, 10/09/2019 | Bosutinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE 
BOSULIF is indicated for the treatment of adult patients with: 
- 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 (14.1)]. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial. 
- Chronic phase, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy. 

2 DOSAGE AND ADMINISTRATION 
2.1 Recommended Dosing 
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. 

If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual prescribed dose on the following day.

2.2 Dose Escalation 
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.

2.5 Dose Adjustments for Renal Impairment or Hepatic Impairment 
The recommended starting doses for patients with renal and hepatic impairment are described in Table 2 below. (See Table 2) 

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. 

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. 

Monitor and manage patients using standards of care. Interrupt, dose reduce or discontinue BOSULIF as necessary [see Dosage and Administration (2.3) and Adverse Reactions (6)].

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

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

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</table>
| 125388, 10/15/2019                     | Brentuximab Vedotin (1) | Oncology | ALK | Clinical Studies |‡ 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. 
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| 125388, 10/15/2019                     | Brentuximab Vedotin (2) | Oncology | TNFRSF8 (CD30) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | as assessed by the central laboratory. Additional efficacy outcomes included CCyR 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 CLINICAL STUDIES
14.2 Systemic Anaplastic Large Cell Lymphoma
Clinical Trial in Relapsed sALCL (Study 2-)
(…) The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had a median of 2 prior therapies; 28% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK) negative. (…) |

14 CLINICAL STUDIES
14.2 Systemic Anaplastic Large Cell Lymphoma and Other CD30-expressing Peripheral T-cell lymphomas (PTCL), in combination with chemotherapy
ADCETRIS is indicated for the treatment of adult patients with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone. ADCETRIS is indicated for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy. |

2 DOSEAGE AND ADMINISTRATION
2.1 Recommended Dosage
For dosing instructions of combination agents administered with ADCETRIS, see Clinical Studies (14.1 and 14.2) and the manufacturer’s prescribing information. (See Table 1) |

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
(…) Data summarizing ADCETRIS exposure are also provided for 347 patients with T-cell lymphoma, including 223 patients with PTCL who received ADCETRIS in combination with chemotherapy in a randomized, double-blind, controlled trial; 58 patients with sALCL who received ADCETRIS monotherapy in a single-arm trial; and 68 patients with pcALCL or CD30-expressing MF who received ADCETRIS monotherapy in a randomized, controlled trial. (…) |

7 USE IN SPECIFIC POPULATIONS
7.5 Geriatric Use
(…) In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHELON-2), 31% of ADCETRIS + CHP-treated patients were age 65 or older. (…) In the clinical trial of ADCETRIS in pcALCL or CD30-expressing MF (Study 4: ALCANZA), 42% of ADCETRIS-treated patients were age 65 or older. No meaningful differences in safety or efficacy were observed between these patients and younger patients. |

14 CLINICAL STUDIES
14.2 Systemic Anaplastic Large Cell Lymphoma and Other CD30-Expressing Peripheral T-cell Lymphomas
Randomized Clinical Trial in Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-cell Lymphomas (Study 6: ECHELON-2, NCT01771752)
The efficacy of ADCETRIS in combination with chemotherapy for the treatment of adult patients with previously untreated, CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. For enrollment, the trial required CD30 expression ≥10% by immunohistochemistry. The trial excluded patients with primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. (See Table 13) (…) |

14.4 Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides
Randomized Clinical Trial in Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA, NCT01578499)
The efficacy of ADCETRIS in patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) requiring systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. (…) Patients with pcALCL must have received prior radiation or systemic therapy, and must have at least 1 biopsy with CD30-expression of ≥10%. Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30-expression of ≥10% in at least 1 biopsy. |
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<tr>
<td>205422, 02/09/2018</td>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>A total of 131 patients were randomized (68 ADCTERIS, 65 physician’s choice). The efficacy results were based on 128 patients (64 patients in each arm with CD30-expression of ≥10% in at least one biopsy). (See Table 15) (…) (…) Supportive trials include 2 single-arm trials, which enrolled patients with MF who were treated with ADCTERIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Out of 73 patients with MF from the 2 pooled supportive trials, 34% (25/73) achieved ORR4. Among these 73 patients, 35 had 1% to 9% CD30-expression and 31% (11/35) achieved ORR4.</td>
</tr>
<tr>
<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>1 INDICATIONS AND USAGE ALUNBRIG is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test [see Dosage and Administration (2.1)].</td>
</tr>
<tr>
<td>205836, 05/12/2018</td>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<th>Biomarker/ Specificity</th>
<th>Labeling Sections</th>
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<tr>
<td>018692, 11/02/2018</td>
<td>Bupivacaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td><strong>WARNINGS</strong></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.</td>
</tr>
<tr>
<td>018692, 11/02/2018</td>
<td>Bupivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific</td>
<td>Warnings</td>
<td><strong>WARNINGS</strong></td>
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<td>(Congenital Methemoglobinemia)</td>
<td></td>
<td>Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.</td>
</tr>
<tr>
<td>018644, 11/05/2019</td>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>(…) Clinical studies (5.4)</td>
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<tr>
<td>0121212021, 21/2688</td>
<td>Cabotegravir and Rilpivirine (1)</td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>1.1 Clinical Trials in Adults</td>
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<td>The efficacy of CABENUVA has been evaluated in two Phase 3 randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials: (…)</td>
</tr>
<tr>
<td>0121212021, 21/2688</td>
<td>Cabotegravir and Rilpivirine (2)</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Potential for WELLBUTRIN to Affect Other Drugs</td>
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<td>Drugs Metabolized by CYP2D6: In vitro, bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion 300 mg/day followed by a single dose of 50 mg desipramine increased the Cmax, AUC, and t1/2 of desipramine by an average of approximately 2, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied: (…)</td>
</tr>
<tr>
<td>203758, 01/31/2020</td>
<td>Cabozantinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
</tr>
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<td>(…) 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 35%. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI: (…)</td>
</tr>
<tr>
<td>029896, 02/22/2019</td>
<td>Capeceitabine</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
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<td>5.4 Dihydropyrimidine Dehydrogenase Deficiency</td>
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<td>Based on postmarketing reports, patients with certain homozgyous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (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 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 DPD activity. No XELODA dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.</td>
</tr>
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<td>213591, 05/06/2020</td>
<td>Capmatinib</td>
<td>Oncology</td>
<td>MET</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TABRECTA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved 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).</td>
</tr>
<tr>
<td>016608, 03/20/2018</td>
<td>Carbamazepine (1)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>BOXED WARNING Serious dermatologic reactions and HLA-B<em>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</em>1502, an inherited allelic variant of the HLA-B gene. HLA-B<em>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</em>1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk (see WARNINGS AND PRECAUTIONS, Laboratory Tests).</td>
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14 CLINICAL STUDIES

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with TABRECTA based on the presence of a mutation that leads to MET exon 14 skipping in tumor specimens [see Clinical Studies (14)]. Information on FDA-approved tests is available at: [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

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Table: Pharmacogenomic Biomarkers in Drug Labeling

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<tr>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>213591, 05/06/2020</td>
<td>Capmatinib</td>
<td>Oncology</td>
<td>MET</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TABRECTA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved 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).</td>
</tr>
<tr>
<td>016608, 03/20/2018</td>
<td>Carbamazepine (1)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>BOXED WARNING Serious dermatologic reactions and HLA-B<em>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</em>1502, an inherited allelic variant of the HLA-B gene. HLA-B<em>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</em>1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk (see WARNINGS AND PRECAUTIONS, Laboratory Tests).</td>
</tr>
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<tr>
<td>016608, 03/20/2018</td>
<td>Carbamazepine (2)</td>
<td>Neurology</td>
<td>HLA-A</td>
<td>Warnings</td>
<td>PRECAUTIONS 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>022562, 12/23/2019</td>
<td>Carglumic Acid</td>
<td>Inborn Errors of Metabolism</td>
<td>NAGS</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Acute hyperammonemia in patients with NAGS deficiency Carbamazepine 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 Carbarglu with other ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction are recommended. 1.2 Chronic Hyperammonemia in Patients with NAGS Deficiency Carbarglu 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.</td>
</tr>
</tbody>
</table>

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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>
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<td>12.3 Pharmacokinetics</td>
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<td></td>
<td>CYP2D6 Poor Metabolizers</td>
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<td>CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.</td>
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<td>Drug Interaction Studies</td>
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<td>CYP2D6 inhibitors</td>
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<td></td>
<td>CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.</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 POPULATION</td>
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<td>8.8 Patients with Reduced CYP2C19 Activity</td>
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<td>Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients [see Clinical Pharmacology (12.3)].</td>
</tr>
<tr>
<td>020297, 08/14/2017</td>
<td>Carvedilol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
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<tr>
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<td>7.1 CYP2D6 Inhibitors and Poor Metabolizers</td>
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<td>Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R (+) enantiomer of carvedilol [see Clinical Pharmacology (12.3)]. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R (+) enantiomer.</td>
</tr>
<tr>
<td>02/25/2021, 213026</td>
<td>Casimersen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
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<td>AMONDYS45 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS45 [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.</td>
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<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trials Experience</td>
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<td>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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>
</tr>
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<tr>
<td>05/03/2019, 020998</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</td>
</tr>
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<tr>
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<td>2.7 Special Populations</td>
<td>Poor Metabolizers of CYP2C9 Substrates</td>
<td>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>
<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.4 Pediatric Use</td>
<td>Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see Poor Metabolizers of CYP2C9 substrates (8.8)].</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
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<tr>
<td></td>
<td>8.8 Poor Metabolizers of CYP2C9 Substrates</td>
<td>In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer Celecoxib starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)].</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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1 INDICATIONS AND USAGE
1.3 Non-Small Cell Lung Cancer
LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR, ALK or ROS1 aberrations, and:
- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- metastatic.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection for NSCLC
Select patients with locally advanced or metastatic NSCLC for treatment with LIBTAYO based on PD-L1 expression on tumor cells [see Clinical Studies (14.3)]. Information on FDA-approved tests for the detection of PD-L1 expression is available at: [link to FDA website].

3 CLINICAL STUDIES
14.3 Non-Small Cell Lung Cancer (NSCLC)
Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; autoimmune disease that required systemic therapy within 2 years of treatment; or who had never smoked were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization. (…)

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</table>
| 050585, 07/12/2018                     | Ceftriaxone (1) | Infectious Diseases | G6PD | Warnings | WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

| 050585, 07/12/2018                     | Ceftriaxone (2) | Infectious Diseases | Nonspecific (Congenital Methemoglobinemia) | Warnings | WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

| 205755, 03/05/2019                     | Ceritinib | Oncology | ALK | 1 INDICATIONS AND USAGE | ZYKADIA® is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

5 WARNINGS AND PRECAUTIONS

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 in Warnings and Precautions (5.1). (…)

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 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, below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies. (…)

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. (…)

Previously Untreated ALK-Positive Metastatic NSCLC

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=185) or chemotherapy plus maintenance chemotherapy (N=187). (…)

Previously Treated ALK-Positive Metastatic NSCLC

The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in ASCEND-2 (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) (…)

14 CLINICAL STUDIES

14.1 Previously Treated ALK-Positive Metastatic NSCLC

The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received previous 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. (…)

14.2 Previously Treated ALK-Positive Metastatic NSCLC

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<td>761052, 12/06/2019</td>
<td>Cerliponase Alfa</td>
<td>Metabolism</td>
<td>TPP1</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Studies</td>
<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. (…) 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 (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastases included brain (60%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 90% of patients. (…)</td>
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<tr>
<td>125084, 04/06/2021</td>
<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>The efficacy of ZYKADIA was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl pep tide 1 (TPP1) deficiency. (…) 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 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 peptide 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)]. Safety and effectiveness in patients less than 3 years of age have not been established.</td>
</tr>
<tr>
<td>125084, 04/06/2021</td>
<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>1 INDICATIONS AND USAGE</td>
<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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<tr>
<td>125084, 04/06/2021</td>
<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
<td>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)]. 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>
<tr>
<td>125084, 04/06/2021</td>
<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>6 ADVERSE REACTIONS</td>
<td>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) (…)</td>
</tr>
</tbody>
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### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2021**

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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>
</tr>
</thead>
<tbody>
<tr>
<td>1250584, 04/06/2021</td>
<td>Cetuximab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>1 INDICATIONS AND USAGE</td>
<td>1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer</td>
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<td>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)]:</td>
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<td>• in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment,</td>
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<td>• in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,</td>
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<td>• 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 Studies (14.2)].</td>
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<td>Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when he results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)].</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.2 Recommended Dosage for Colorectal Cancer (CRC)</td>
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<td>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 CRC is available at: <a href="http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invdiagnostics/uscm301431.htm">http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invdiagnostics/uscm301431.htm</a>.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC</td>
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<td>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)].</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>K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)</td>
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<td>In Combination with FOLFIRI</td>
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<td>(…) The safety of a cetuximab product in combination with FOLFIRI alone was evaluated in CRISTAL. The data described below reflect exposure to cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. [See Table 4] (…)</td>
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<td>As Single-Agent</td>
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<td>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) (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)</td>
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<td>In Combination with FOLFIRI</td>
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<tr>
<td>020989, 12/08/2006</td>
<td>Cevimeline</td>
<td>Dental, Gastroenterology</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>K-Ras mutation 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. 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) As Single-Agent 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.</td>
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<tr>
<td>006002, 10/24/2018</td>
<td>Chloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS: Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an in vitro study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline.</td>
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<tr>
<td>011841, 02/01/2011</td>
<td>Chlorpropamide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS: Methemoglobinemia is recommended.</td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine</td>
<td>Anaesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.</td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine</td>
<td>Anaesthesiology</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, CYP1A1, CYP2A1, DHC9, HSD3B2 (Bile Acid Synthesis Disorders)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: 1.1 Bile Acid Synthesis Disorders Due to Single Enzyme Defects CHOLBAM is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs). 1.3 Limitations of Use: The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established. 2 DOSAGE AND ADMINISTRATION: 2.1 Dosage Regimen for Bile Acid Synthesis Disorders Due to SEDs and PDs Including Zellweger Spectrum Disorders: The recommended dosage of CHOLBAM is 10 to 15 mg/kg administered orally once daily or in two divided doses, in pediatric patients and adults. 2.2 Treatment Monitoring: Assessment of serum or urinary bile acid levels using mass spectrometry is used in the diagnosis of bile acid synthesis disorders due to SEDs and PDs including Zellweger spectrum disorders. The utility of bile acid measurements in monitoring the clinical course of patients and in decisions regarding dose adjustment has not been demonstrated.</td>
</tr>
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</table>

5 WARNINGS AND PRECAUTIONS
5.1 Exacerbation of Liver Impairment
In clinical trials, evidence of liver impairment was present before treatment with CHOLBAM in approximately 86% (44/51) of patients with bile acid synthesis disorders due to SEDs and in approximately 50% (14/28) of patients with PDs including Zellweger spectrum disorders. Five of the patients (3 SED and 2 PD) with liver impairment at baseline experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy following treatment. Five additional patients (2 SED and 3 PD) who did not have baseline cholestasis experienced exacerbation of their liver disease while on treatment. In patients with cirrhosis, cases of severe hepatotoxicity have also been observed following postmarket use of CHOLBAM. Exacerbation of liver impairment by CHOLBAM in these patients cannot be ruled out.

Six patients with SEDs underwent liver transplant, including four patients diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency, and one with CYP7A1 deficiency. (…)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Clinical safety experience with CHOLBAM consists of:
- Trial 1: a non-randomized, open-label, single-arm trial of 50 patients with bile acid synthesis disorders due to SEDs and 29 patients with PDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.
- Trial 2: an extension trial of 12 new patients (10 SED and 2 PD) along with 31 (21 SED and 10 PD) patients who rolled over from Trial 1. Safety data are available for 3 years and 11 months of treatment. (…)

Deaths
In Trial 1, among the 50 patients with SEDs, 5 patients aged 1 year or less died, which included three patients originally diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency and one with CYP7A1 deficiency. The cause of death was attributed to progression of underlying liver disease in every patient. Of 29 patients in Trial 1 with PDs including Zellweger spectrum disorders, 12 patients between the ages of 7 months and 2.5 years died. In the majority of these patients (8/12), the cause of death was attributed to progression of underlying liver disease or to a worsening of their primary illness.

Two additional patients in Trial 1 (1 SED and 1 PD) died who had been off study medication for more than one year with the cause of death most likely being a progression of underlying liver disease. Of the patients who died with disease progression, laboratory testing showed abnormal serum transaminases, bilirubin, or cholestasis on liver biopsy suggesting worsening of their underlying cholestasis. In Trial 2, among the 31 patients with SED, two patients (1 new patient and 1 who rolled over from Trial 1) died. The cause of death in both cases was unrelated to their primary treatment or progression of their underlying liver disease. Of the 12 patients with PD in Trial 2, four patients died between the ages of 4 and 8 years (1 new patient and 3 who rolled over from Trial 1). The cause of death in three of these patients was attributed to progression of underlying liver disease or to a worsening of their primary illness.

Worsening of Liver Impairment
Seven patients in Trial 1 (4 SED and 3 PD) and 3 patients in Trial 2 (1 SED and 2 PD) experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy during treatment [see Warnings and Precautions (5.1)].

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of CHOLBAM have been established in pediatric patients 3 weeks of age and older for the treatment of bile acid synthesis disorders due to SEDs and for adjunctive treatment of patients with PDs including Zellweger spectrum disorders who exhibit manifestations of liver disease, steatorrhea, or complications from decreased-fat-soluble vitamin absorption [see Clinical Studies (14)].

14 CLINICAL STUDIES
14.1 Bile Acid Synthesis Disorders due to Single Enzyme Defects
The effectiveness of CHOLBAM at dosages of 10 to 15 mg/kg per day in patients with SEDs was assessed in:
- Trial 1: a non-randomized, open-label, single-arm trial in 50 patients over an 18-year period
- Trial 2: an extension trial of 12 new patients along with 21 patients who rolled over from Trial 1 (n=33 total). Efficacy data are available for 21 months of treatment.

A published case series of 15 patients with SEDs and 3 patients with PDs. (…)

Trials 1 and 2
On average, patients were 4 years of age at the start of cholic acid treatment (range three weeks to 36 years). The majority of patients were treated for an average of 310 weeks (6 years). Patient ages at the end of treatment ranged from 19 to 36 years.

Overall, 28 of 44 patients (64%) were responders. The breakdown by defect type is as follows: (See Table 4). Among SED responsive patients, 45% of the responders met the two clinical criteria plus 1 to 3 laboratory criteria and 55% met the weight criteria.

Only six patients had pre- and post-treatment liver biopsies in Trial 1. Where biopsies were available, pre-treatment biopsies showed varying degrees of inflammation, bridging fibrosis, and giant cell formation. Post-treatment biopsies generally showed reduced or absent inflammation and reduced or absent giant cell formation. Fibrosis remained but did not progress.

It is difficult to evaluate long-term survival in patients with SEDs since there is little natural history survival data for comparison. Overall, 41 of 62 (67%) patients with SEDs survived greater than 3 years from trial entry. Thirteen of these 41 patients (32%) survived for 10 to 24 years on treatment. Four patients in Trial 1 underwent liver transplant, including two patients diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency, and one with CYP7A1 deficiency and two patients in Trial 2, both with AKR1D1.

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<td>Cisplatin (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS</td>
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<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>
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<td>Citalopram (1), 01/11/2019</td>
<td>Citalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>DOSAGE AND ADMINISTRATION</td>
<td>Special Populations</td>
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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 Pointes</td>
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<td>The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected.</td>
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<td>CLINICAL PHARMACOLOGY</td>
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<td>Pharmacokinetics</td>
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<td>Population Subgroups</td>
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<td>(…) CYP2C19 poor metabolizers – In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Clexa 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).</td>
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<td>CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.</td>
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<td>Psychiatry</td>
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<td>Drug-Drug Interactions</td>
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<td>Coadministration of a drug that inhibits CYP2D6 with Clexa is unlikely to have clinically significant effects on citalopram metabolism, based on the study results in CYP2D6 poor metabolizers.</td>
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<tr>
<td>Clobazam, 06/15/2018</td>
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<td>Neurology</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
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<td>2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers</td>
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<td>In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam’s active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 (see Use in Specific Populations (8.6), Clinical Pharmacology (12.5)).</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>Concentrations of clobazam’s active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended (see Dosage and Administration (2.5), Clinical Pharmacology (12.3)).</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Metabolism and Excretion</td>
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<td>(…) The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethyliclobazam [see Clinical Pharmacology (12.5)]. In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.</td>
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<td>12.5 Pharmacogenomics</td>
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<td>The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethyliclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethyliclobazam AUC and Cmax are approximately 3-5 times higher in poor metabolizers (e.g., subjects with *2/*2 genotype) and 2-3 times higher in extensive metabolizers (e.g., subjects with *1/*1 genotype).</td>
</tr>
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<td>Clomipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>higher in intermediate metabolizers (e.g., subjects with *1/*2 genotype). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted [see Dosage and Administration (2.5)]. The systemic exposure of clozapine is similar for both CYP2C19 poor and extensive metabolizers.</td>
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<td>020839, 05/17/2019</td>
<td>Clopidogrel</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Boxed Warning, Warnings and Precautions, Clinical Pharmacology</td>
<td>BOXED WARNING</td>
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<tr>
<td>019758, 02/23/2017</td>
<td>Clozapine</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>206192, 01/26/2018</td>
<td>Cobimetinib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>02/2402, 09/18/2018</td>
<td>Codeine</td>
<td>Anesthesia</td>
<td>CYP2D6</td>
<td>6.1 Clinical Trials Experience (…) The safety of COTELLIC was evaluated in Trial 1, a randomized (1:1), double blind, active-controlled trial in previously untreated patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma [see Clinical Studies (14)]. (…)</td>
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<td>14 CLINICAL STUDIES The safety and efficacy of cobimetinib was established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation test. (…) (…) The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review. A trend favoring the cobimetinib with vemurafenib arm was observed in exploratory subgroup analyses of PFS, OS, and ORR in both BRAF V600 mutation subtypes (V600E or V600K) in the 81% of patients in this trial where BRAF V600 mutation type was determined.</td>
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<td>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 a ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism [see Warnings and Precautions (5.4)]. Codeine Sulfate Tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see Contraindications (4)). Avoid the use of Codeine Sulfate Tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. (…)</td>
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<td>5 WARNINGS AND PRECAUTIONS 5.4 Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. (…) Nursing Mothers At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Codeine Sulfate Tablets [see Use in Specific Populations (8.2)]. CYP2D6 Genetic Variability: Ultra-Rapid Metabolizers Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as “1/*1xN” or “1/*2xN”). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)]. Therefore, individuals who are ultra-rapid metabolizers should not use Codeine Sulfate Tablets.</td>
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<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 adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine. (…)</td>
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<td>17 PATIENT COUNSELING INFORMATION Ultra-Rapid Codeine Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children</td>
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<td>HBB</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
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<td>1. Clinical Trials Experience</td>
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<td>Sickle Cell Disease</td>
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<td>The safety of ADAKVEO was evaluated in the SUSTAIN trial [see Clinical Studies (14.1)]. Eligible patients were diagnosed with sickle cell disease (any genotype including HbSS, HbSC, HbS beta0-thalassemia, HbS beta+ thalassemia, and others). (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>The efficacy of ADAKVEO was evaluated in patients with sickle cell disease in SUSTAIN [NCT01895361], a 52-week, randomized, multicenter, placebo-controlled, double-blind study. A total of 198 patients with sickle cell disease, any genotype (HbSS, HbSC, HbS beta 0-thalassemia, HbS beta + thalassemia, and others), and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. (See Table 2) (…) (…)</td>
</tr>
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**ALK- or ROS1-Positive Metastatic NSCLC**

The recommended dosage of XALKORI in patients with severe renal impairment (creatinine clearance (CLcr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation) or not requiring dialysis is 250 mg orally once daily (see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

Systemic ALK-positive ALC

The recommended dosage of XALKORI in patients with severe renal impairment (CLcr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients not requiring dialysis is the second dose reduction based on BSA as shown in Table 2 (see Dosage and Administration (2.5), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

**2.8 Dosage Modification for Concomitant Use of Strong CYP3A Inhibitors**

ALK- or ROS1-positive metastatic NSCLC

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

**Systemic ALK-positive ALCL**

Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to the second dose reduction based on BSA as shown in Table 2 (see Dosage and Administration (2.5), Drug Interactions (7.1)). After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

(…)
The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients with NSCLC 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 also reflect exposure to XALKORI in 121 patients ages 1 to 21 years with relapsed or refractory tumors, including 26 patients with systemic ALC, in a single-arm trial (Study ADV0912).

ALK- or ROS1-Positive Metastatic NSCLC

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

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014)

The data in Table 3 are derived from 340 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 12 months of age and older with relapsed or refractory, systemic ALCL (see Adverse Reactions (6.1), Clinical Studies (14.2)). The safety and effectiveness have not been established in pediatric patients younger than 12 months of age with ALCL or in any pediatric patients with NSCLC.

In a study that evaluated XALKORI in combination with chemotherapy in pediatric patients with newly diagnosed ALCL (Study ANHL12P1; NCT01979536), 13 of 66 (20%) patients had a Grade 2 or higher thromboembolic event, including pulmonary embolism in 6%. The safety and effectiveness of XALKORI in combination with chemotherapy have not been established in patients with newly diagnosed ALCL.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of XALKORI have been established in pediatric patients 12 months of age and older with relapsed or refractory, systemic ALK-positive ALC (see Adverse Reactions (6.1), Clinical Studies (14.2)). The safety and effectiveness have not been established in pediatric patients younger than 12 months of age with ALCL or in any pediatric patients with NSCLC.

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<td>Crizotinib (2)</td>
<td>Oncology</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
</tr>
</tbody>
</table>

1 INDICATIONS AND USAGE
1.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer
XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)].

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Warnings and Precautions (5.3)].

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<td>BRAF</td>
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<td>INDICATIONS AND USAGE</td>
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<td></td>
<td>1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma</td>
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<td>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)].</td>
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<td>1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma</td>
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<td>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)].</td>
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<td>1.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma</td>
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<td>TAFINLAR is indicated, in combination with trametinib, for the 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)].</td>
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<td>1.4 BRAF V600E Mutation-Positive Metastatic NSCLC</td>
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<td>TAFINLAR is indicated, in combination with trametinib, for the treatment of 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)].</td>
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<td>1.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer</td>
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<td>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)].</td>
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</table>

#### 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

**Melanoma**
- 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/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Clinical Studies (14.4)].
- 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 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 586 patients with various solid tumors and exposure to TAFINLAR administered with trametinib in 559 patients with melanoma and 93 patients with NSCLC. The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600E mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 300 mg). Metastatic or Unresectable BRAF V600E 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 453 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)]. (…)

#### 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 V600E 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). (…)

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#### 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 IRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis.

**BREAK-MB**

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

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

COBIM-d Study and COBIM-v Study

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

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

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

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

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

**COMBIM-MB Study**

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

**14.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma**

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

(…) In COBIM-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 IIIC (18%), Stage IIIb (33%), Stage IIIA (38%), Stage II (11%), Stage I (3%), Stage U (1%). (…)

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

In Study BRF0113926 (NCT13336354), 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 TAFINLAR administered with trametinib was evaluated in Study BRF0117019 (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

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<td>14.2 Clinical Trials in HCV Genotype 3 (ALLY-3)</td>
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<td>(…) 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 antiretroviral therapy, HCV treatment history, age, gender, IL28B allele status, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…)</td>
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<td>(…) 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. (…) SVR12 rates were comparable regardless of antiretroviral therapy, HCV treatment history, age, race, gender, IL28B allele status, HCV genotype 1 subtype, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…)</td>
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<td>(…) 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, 77% had IL28B rs12979860 non-CC genotype. (…)</td>
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<td>EGFR</td>
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<td>(…) 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). (…)</td>
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<td>Dapsone (1)</td>
<td>Dermatology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS 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. 5.6 Wild-type IL28B (Non-responder) IL28B CC genotype carriers. 5.7 Women of child-bearing potential. 5.8 Pregnancy or lactation. 5.9 Treatment in patients who have accumulated resistance to HCV. 5.10 Use of ACZONE® Gel in patients with a history of severe cutaneous adverse reactions to topically applied products, including those containing benzoyl peroxide. 5.11 Phototoxicity. 5.12 Topical Use. 5.13 Pregnancy. 5.14 Lactation. 5.15 Use in Specific Populations 5.15.1 Children. 5.15.2 Geriatric Use. 5.16 Treatment of cutaneous disease in patients who are immunocompromised or who have received organ transplantation. 5.17 Interactions. 5.18 Pregnancy and Lactation. 5.19 Laboratory Tests. 5.20 Antitumoral Activity. 5.21 Hematologic Effects. 5.22 Metabolism and Excretion. 5.23 Adverse Reactions. 5.24 Overdosage. 5.25 Preclinical Safety Data. 5.26 Clinical Pharmacology. 5.27 Clinical Studies. 8 USE IN SPECIFIC POPULATIONS 8.1 Children. 8.2 Lactation Risk. 8.3 Renal Impairment. 8.4 Hematological Effects. 8.5 Use in Specific Populations. 8.6 G6PD Deficiency.</td>
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<td>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 QTc 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 median HR following treatment with Enablex was no different from placebo.</td>
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| 02/19/86, 12/21/2018  | Dasatinib          | Oncology          | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific | 1 INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients 1 year of age and older with Ph+ CML in chronic phase. newly diagnosed Ph+ ALL in combination with chemotherapy.

206/619, 07/23/2018 Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir Infectious Diseases IFNL3 (IL28B) Clinical Studies

14 CLINICAL STUDIES

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 VEIKIRA PAK with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV [see Clinical Studies (14.1)].

- Mean 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; 15% 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 Chronic HCV GT1b Infection without Cirrhosis

Subjects with HCV GT1b infection without cirrhosis treated with VEIKIRA PAK with or without RBV for 12 weeks in PEARL-II and -III [see Clinical Studies (14.1)].

- Mean 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

(…). Treated subjects had a median age of 53 years (range: 21 to 71); 70% of the subjects were male; 81% were White; 7% were Black/African American; 12% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m²; 43% of patients were enrolled in US sites; 82% had IL28B (rs12979860) non-CC genotype; 86% had baseline HCV RNA levels of at least 800,000 IU per mL; 69% had HCV GT1a infection; 31% had HCV GT1b infection; 42% were treatment-naïve; 36% were prior pegIFN/RBV null responders; 6% were prior pegIFN/RBV partial responders; 14% were prior pegIFN/RBV relapers; 15% had platelet counts of less than 90 x 10⁹ per L; 50% had albumin less than 4.0 mg per dL. (…)

14.4 Clinical Trial Results 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; 53% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection. (…)

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<td>Populations, Clinical Studies</td>
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**2.1 Dosage of SPRYCEL in Adult Patients**
The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

**2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL**
The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary. (See Table 1)

Refer to Section 2.4 for recommendations on dose escalation in adults in CML and Ph+ ALL, and pediatric patients with CML.

**2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML**
For adult patients with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2 below). Dose escalation is not recommended for pediatric patients with Ph+ ALL, where SPRYCEL is administered in combination with chemotherapy. Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients with chronic phase CML who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. (See Tables 2, 3, and 4)

**2.5 Dose Adjustment for Adverse Reactions**

**Myelosuppression**
(…)

For pediatric patients with Ph+ ALL, if neutropenia and/or thrombocytopenia result in a delay of the next block of treatment by more than 14 days, interrupt SPRYCEL and reduce the same dose level once the next block of treatment is started. (…)

**Non-Hematologic Adverse Reactions**
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 [see Warnings and Precautions (5.1)]. 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 adult 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 MMR.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 [see Dosage and Administration (2.2) and Clinical Studies (14.4)]. 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+ CML 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 38%. Among the 1618

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<td></td>
<td>SPRYCEL</td>
<td>Oncology</td>
<td>IL2RA</td>
<td>Sections</td>
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|                                   |                    |                  | (CD25 antigen) |                 | SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation 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 discontinuation were reported in 191 (17.5%) patients. (…) Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults A total of 135 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 multishort 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 to 27 months). (See Tables 14 and 15) (…) Additional Pooled Data From Clinical Trials The following additional adverse reactions were reported in patients in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These events are included on the basis of clinical relevance. 8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use Ph+ CML in Chronic Phase The safety and effectiveness of SPRYCEL monozoney 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 Difficultly 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 (MoCR; after 6 months), or complete cytogenetic response (CoCR; 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 CoCR, defined as elimination (CoCR) 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 median of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twicedaily 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. (…) * 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. ‡ Blue text represents the most recent additions and/or changes since last posted version.
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| 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 enzymatic activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tetracyclic 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). (…) |
| 020118, 03/01/2019                     | Desflurane | Anesthesiology | Non-specific (Genetic Susceptibility to Malignant Hyperthermia) | Contraindications | 4 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 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
|                                        |      |                   |           |                  | 12.3 Pharmacokinetics
|                                        |      |                   |           |                  | Metabolism and elimination
|                                        |      |                   |           |                  | Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 2D6 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. (…) |
| 208082, 06/06/2018                     | Deutetrabenazine | Neurology | CYP2D6 | Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
|                                        |      |                   |           |                  | 2.4 Dose Adjustment in Poor CYP2D6 Metabolizers
|                                        |      |                   |           |                  | In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Use in Specific Populations (8.7)]. |
|                                        |      |                   |           |                  | 5 Warnings and Precautions
|                                        |      |                   |           |                  | 5.7 QTc Prolongation
|                                        |      |                   |           |                  | (…) A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizers or co-administered a strong CYP2D6 inhibitor [see Clinical Pharmacology (12.2, 12.3)]. 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)]. 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)]. (…) |
| 022287, 06/07/2018                     | Dextansaoprazole | Gastroenterology | CYP2C19 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS
|                                        |      |                   |           |                  | Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. |

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<tr>
<td>O21879, 06/11/2019</td>
<td>Dextromethorphan and Quinidine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Warnings and Preventions, Clinical Pharmacology</td>
<td>(...) 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). Dextromethorphan 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 dextromethorphan and its glucuronide conjugate, while in CYP2C19 poor metabolizers dextromethorphan sulfone is the major plasma metabolite. Cytchrome P 450 Interactions (...) Although in vitro studies indicated that DEXILANT has the potential to inhibit CYP2C19 in vivo, in 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). (...) Clotiprodigro Clopidigrolo 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 clopidigrolo 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 clopidigrolo was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 85-97%) when DEXILANT was coadministered compared to administration of clopidigrolo alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 μM ADP) was related to the change in the exposure to clotiprodigrolo active metabolite. The effect on exposure to the active metabolite of clotiprodigrolo and on clotiprodigrolo-induced platelet inhibition is not considered clinically important. 12.5 Pharmacogenomics Effect of CYP2C19 Polymorphism on Systemic Exposure of Dextromethorphan Systemic exposure of dextromethorphan is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of DEXTILANT 30 mg or 60 mg capsules (N=2 to 6 subjects/group), mean dextromethorphan Cmax and AUC values were up to two times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean Cmax was up to four times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dextromethorphan exposure in these races will be affected by CYP2C19 phenotypes as well.</td>
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<tr>
<td>020648, 12/16/2016</td>
<td>Diazepam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination (...) The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are &quot;poor metabolizers&quot;) and CYP3A4. (...)</td>
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<td>125516, 03/01/2017</td>
<td>Dinutuximab</td>
<td>Oncology</td>
<td>MYCN</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (...) Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. (...)</td>
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<tr>
<td>022234, 10/11/2019</td>
<td>Docetaxel</td>
<td>Oncology</td>
<td>ESR, PGR</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Adjuvant Treatment of Breast Cancer (...) Docetaxel was administered as a 3-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 1A) (...)</td>
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<td>204790, 09/06/2018</td>
<td>Dolutegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>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).</td>
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<td>020690, 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 (63%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. 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>
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<td>042222021, 761174</td>
<td>Dostarlimab-gxly</td>
<td>Oncology</td>
<td>Mismatch Repair</td>
<td>Indication and Usage JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed or following prior treatment with platinum-containing regimen [see Dosage and Administration (2.4)]. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Mismatch Repair Deficient (dMMR) Advanced Endometrial Cancer Select patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen for treatment with JEMPERLI based on the presence of dMMR in tumor specimens [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of dMMR status is available at <a href="http://www.fda.gov/CompanionDiagnoses">http://www.fda.gov/CompanionDiagnoses</a>. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Mismatch Repair Deficient (dMMR) Endometrial Cancer The safety of JEMPERLI was evaluated in the GARNET trial in 104 patients with advanced or recurrent dMMR EC who received at least one dose of JEMPERLI [see Clinical Studies (14)]. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Among patients receiving JEMPERLI, 47% were exposed for 6 months or longer and 20% were exposed for &gt;1 year. (See Tables 2 and 3) (...) 14 CLINICAL STUDIES The efficacy of JEMPERLI was evaluated in the GARNET study (NCT02715284), a multicenter, multicohort, open-label study conducted in patients with advanced solid tumors. The efficacy population consisted of a cohort of 71 patients with mismatch repair deficient (dMMR) recurrent or advanced EC who had progressed on or after treatment with a platinum-containing regimen. Patients with prior treatment with PD-1/PD-L1–blocking antibodies or other immune checkpoint inhibitor therapy and patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 2 years were excluded from the study. The baseline characteristics were: median age 64 years (49% aged 65 years or older); 82% White, 3% Asian, 1% Black; and Eastern Cooperative Oncology Group Performance Status 0 (52%) or 1 (68%). At time of study entry, 66% of the patients with dMMR EC had International Federation of Gynecology and Obstetrics (FIGO) Stage IV disease. The most common histology seen was endometrioid carcinoma type 1 (70%), followed by serous (6%) and mixed and undifferentiated (2.8% each). All patients with dMMR EC had received prior anticancer treatment, with 90% of patients receiving prior anticancer surgery and 78% receiving prior anticancer radiotherapy. Approximately 40% had 2 lines or more of prior anticancer treatment. Approximately 11% of patients had received 3 regimens and 4% had received 4 or more prior regimens. The dMMR tumor status was retrospectively confirmed using the VENTANA MMR RxDx Panel assay. (See Table 4)</td>
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<td>CYP2D6</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>Poor Metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
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<td>02/2036, 03/17/2010</td>
<td>Dopepine (2)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>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>8 USE IN SPECIFIC POPULATIONS</td>
<td>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>
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<td>02/1676, 08/09/2017</td>
<td>Drospirenone and Ethinyl Estradiol</td>
<td>Gynecology</td>
<td>CYP2C19</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.5 Pharmacoemogenomics Published data indicate a 2- to 3-fold higher dronabinol exposure in individuals carrying genetic variants associated with diminished CYP2C9 function.</td>
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<tr>
<td>02/1427, 12/19/2017</td>
<td>Duloxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>7 DRUG INTERACTIONS</td>
<td>Duloxetine plasma concentrations may be increased by coadministration of drugs that increase dextromethorphan plasma levels, such as ketoconazole, erythromycin, cimetidine, or astemizole. (See Clinical Pharmacology (12.3).)</td>
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<tr>
<td>761069, 06/05/2020</td>
<td>Durvalumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>Poor Metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
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<tr>
<td>211155, 09/26/2019</td>
<td>Duvelisib</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>14 CLINICAL STUDIES</td>
<td>14.1 Efficacy in Relapsed or Refractory CLL/SLL Study 1 (…). In this subset (95 randomized to COPIKTTRA, 101 to ofatumumab), the median patient age was 69 years (range: 40 to 90 years), 59% were male, and 88% had an ECOG performance status of 0 or 1. Forty-six percent received 2 prior lines of therapy, and 54% received 3 or more prior lines. At baseline, 52% of patients had at least one tumor ≥ 5 cm, and 22% of patients had a documented 17p deletion. (…)</td>
</tr>
<tr>
<td>125166, 06/27/2019</td>
<td>Eculizumab (1)</td>
<td>Neurology</td>
<td>ACHR</td>
<td>1 INDICATIONS AND USAGE</td>
<td>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.</td>
</tr>
</tbody>
</table>

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<td>Elagolix</td>
<td>CYP2B6</td>
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<td>Clinical Pharmacology</td>
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<tr>
<td>02/09/2017</td>
<td>Efavirenz</td>
<td>IFN3</td>
<td>Infectious Diseases</td>
<td>Pharmacology</td>
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<tr>
<td>2019/06/07/2019</td>
<td>Elbasvir and</td>
<td>IL28B</td>
<td>Infectious Diseases</td>
<td>Pharmacology</td>
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<td></td>
<td>Grazoprevir</td>
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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. If 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 IVlg within 3 weeks prior to screening.

210450, 07/23/2018
Elagolix
Gynecology
SLCO1B1
Clinical Pharmacology

208261, 06/28/2018
Elbasvir and Grazoprevir
Infectious Diseases
IFN3 (IL28B)
Clinical Studies

14.2 Clinical Trials in Treatment-Naive Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE CONFICTION)
(…)
C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naive subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized in a 3:1 ratio; 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; 67% had non-C/C IL28B alleles (CT or TT); and 55% had genotype 1a and 45% had genotype 1b chronic HCV infection.

C-EDGE CONFICTION was an open-label, single-arm trial in treatment-naive HCV/HIV-1 coinfected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks. Among subjects with genotype 1 infection, the median age was 50 years (range: 21 to 71); 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/m²; 59% had baseline HCV RNA levels greater than 600,000 IU per mL; 16% had cirrhosis; 65% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection.

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

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

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<td>212273, 10/21/2019</td>
<td>Eltezacoffor, Ivaacorrh, and Tezaacorrh</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)]. …</td>
</tr>
<tr>
<td>205494, 08/29/2018</td>
<td>Eliglistat</td>
<td>Inborn Errors of Metabolism</td>
<td>CYP2D6</td>
<td>1 INDICATIONS AND USAGE</td>
<td>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)].</td>
</tr>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Absorption</td>
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|                                        |      |                  |            |                  | 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 (AUC(0-12)) increased up to about 2-fold at steady state compared to after the first dose (AUC(0-∞)). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7-fold to 9-fold higher in PMs. Dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted Cmax and AUC0-24hr in PMs also being a pharmacologically based pharmacokinetic (PBPK) model with 84 mg once daily were 75 ng/mL and 956 hr ∙ ng/mL, respectively. Table 7 describes the pharmacokinetic parameters for eliglustat in healthy subjects following multiple doses of 84 mg CERDELGA twice daily. (See Table 7) Administration of CERDELGA with a high fat meal (approximately 1000 calories with 50% calories from fat) resulted in a 10% decrease in Cmax (not clinically significant) but no change in AUC. Distribution Following intravenous administration, the volume of distribution of eliglustat was 835 L in EMs. Plasma protein binding of eliglustat ranges from 76% to 83%. Elimination Eliglustat terminal elimination half-life was approximately 6.5 hours in CYP2D6 EMs, and 8.9 hours in PMs. Following intravenous administration of 42 mg (0.5 times the recommended oral dose) in healthy subjects, the mean (range) of eliglustat total body clearance was 88 L/h (80 to 105 L/h) in EMs. Specific Populations No clinically significant differences in the pharmacokinetics of eliglustat were observed based on age (18 to 71 years), sex, race (mostly were Caucasian, including those of Ashkenazi Jewish descent; however, it included the following populations: African American, American Indians, Hispanics, and Asians), or body weight (41 to 136 kg). Patients with renal impairment Eliglustat pharmacokinetics was similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs. Eliglustat pharmacokinetics in EMs with ESRD and in EMs 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 135% and 110% for Cmax and 171% and 121% for AUC in CYP2D6 EMs with mild and moderate hepatic impairment, respectively. (See Table 8) Steady-state pharmacokinetics of eliglustat in CYP2D6 PMs 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)). 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 PMs, respectively [see Drug Interactions (7.2)]. P-gp substrates Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage) in CYP2D6 EMs and PMs, 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 (…). The CERDELGA treatment group was comprised of IM (5%), EM (80%) and URM (5%) patients. (…) 1 INDICATIONS AND USAGE Vimizim (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). 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. 5.3 Spinal or Cervical Cord Compression 125460, 02/14/2014 Elosulfase Inborn Errors of Metabolism GALNS Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies

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<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.3 Thrombotic/Thromboembolic Complications</td>
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<td>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>SERPINC1 (Antithrombin III)</td>
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<td>5.3 Thrombotic/Thromboembolic Complications</td>
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<td>Chromosome 7</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>Cytogenetic Abnormalities</td>
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<td>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 clonal abnormalities 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 therapy, including 5 patients who had complex changes in chromosome 7. (…)</td>
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<td>Hematology</td>
<td>PRF1, RAB27A, SH2D1A, STXB2, STX11, UNC13D, XIAP (Hemophagocytic Lymphohistiocytosis)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>(…) A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FHL3-UNC13D (MUNC 13-4) (26%), FHL2-PRF1 (1%), and Griscelli Syndrome type 2 (19%). The HLH mutations in the population enrolled are described in Table 3. (See Table 3)</td>
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</table>
| 209608, 09/27/2019                     | Enasidenib      | Oncology        | IDH2       | Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Acute Myeloid Leukemia
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. |

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of AML with IDHIFA based on the presence of IDH2 mutations in the blood or bone marrow [see Indications and Usage (1.1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage
IDHIFA is indicated for the treatment of adult patients with relapsed or refractory AML and an IDH2 mutation, who were assigned to receive 100 mg daily dose. Cohort 1 included 101 patients and Cohort 2 included 98 patients. IDH2 mutations were identified by a local diagnostic test and retrospectively confirmed by the Abbott RealTime™ IDH2 assay, or prospectively identified by the Abbott RealTime™ IDH2 assay, which is the FDA-approved test for selection of patients with AML, for treatment with IDHIFA. (See Table 4) (…) Efficiency was established on the basis of the rate of complete response (CR)/complete response with partial hematologic recovery (CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 5 and were similar in both cohorts. The median follow-up was 6.6 months (range, 0.4 to 27.7 months). Similar CR/CRh rates were observed in patients with either R140 or R172 mutation. (See Table 5) (…) |

14 CLINICAL STUDIES
14.1 Acute Myeloid Leukemia
The efficacy of IDHIFA was evaluated in an open-label, single-arm, multicenter, two-cohort clinical trial (Study AG221-C-001, NCT01915498) of 199 adult patients with relapsed or refractory AML and an IDH2 mutation, who were assigned to receive 100 mg daily dose. Cohort 1 included 101 patients and Cohort 2 included 98 patients. IDH2 mutations were identified by a local diagnostic test and retrospectively confirmed by the Abbott RealTime™ IDH2 assay, or prospectively identified by the Abbott RealTime™ IDH2 assay, which is the FDA-approved test for selection of patients with AML, for treatment with IDHIFA. (See Table 4) (…) Efficiency was established on the basis of the rate of complete response (CR)/complete response with partial hematologic recovery (CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 5 and were similar in both cohorts. The median follow-up was 6.6 months (range, 0.4 to 27.7 months). Similar CR/CRh rates were observed in patients with either R140 or R172 mutation. (See Table 5) (…) |

210406, 04/08/2020  Encorafenib (1) Oncology | BRAF | 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 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
BRAFV600E 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)]. |

1.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
BRAFV600E 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)]. |

1.3 Limitations of Use
BRAFV600E is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC [see Warnings and Precautions (5.2)]. |

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAF TOVI [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: http://www.fda.gov/CompanionDiagnostics. |

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
Confirm the presence of a BRAF V600E mutation in tumor specimens prior to initiating BRAF TOVI [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 BRAF V600E is 450 mg (six 75 mg capsules) orally once daily in combination with binimetinib until disease progression or unacceptable toxicity. Refer to the binimetinib prescribing information for recommended binimetinib dosing information. |

2.3 Recommended Dosage for BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
The recommended dosage of BRAF V600E 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
BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
* 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.
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| 210496, 04/08/2020                     | Encorafenib (2)    | Oncology         | RAS        | Dosage and Administration, Warnings and Precautions, Clinical Studies | 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 BRAF TOVI are presented in Table 1. BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) If cetuximab is discontinued, discontinue BRAF TOVI. Dose reductions for adverse reactions associated with BRAF TOVI 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 BRAF TOVI 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 BRAF TOVI. (…) 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 BRAF TOVI [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 BRAF TOVI in combination with binimetinib is described in 98 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAF TOVI (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 BRAF TOVI 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 690 patients with BRAF mutation-positive melanoma who received BRAF TOVI 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 BRAF TOVI 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 BRAF TOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT0198453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. (…) Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%). (…) 14.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) BRAF TOVI in combination with cetuximab was evaluated in a randomized, open-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen BRAF V600E RQ polymerase chain reaction (PCR) Kit, with disease progression after 1 or 2 prior regimens. (…) 6.1 Clinical Trials Experience BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma (…) The safety of BRAF TOVI in combination with binimetinib is described in 98 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAF TOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS). 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| 761137, 12/18/2019                     | Enfortumab vedotin-ejv | Oncology     | NECTIN4     | Clinical Studies | 14 CLINICAL STUDIES 
14.1 Metastatic Urothelial Cancer 
(...)

The median age was 69 years (range: 40 to 84 years), 70% were male, and 85% were Caucasian. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (32%) or 1 (68%). Ninety percent of patients had visceral metastases including 40% with liver metastases. Two-thirds of patients had pure transitional cell carcinoma (TCC) histology, 33% had TCC with other histologic variants. An immunohistochemistry clinical trial assay was used to assess patients with tumor tissue available, and detected Nectin-4 expression in all patients tested (n=120). (…)

14.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) 
BRAF/VOI was in combination with cetuximab was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen BRAF V600E RQ polymerase chain reaction (PCR) Kit, with disease progression after 1 or 2 prior regimens. Other key eligibility criteria included absence of prior treatment with a RAF, MEK, or EGFR inhibitor, eligibility to receive cetuximab per local labeling with respect to tumor RAS status, and ECOC performance status (PS) 0-1. (…)

1 INDICATIONS AND USAGE 
1.1 ROS1-Positive Non-Small Cell Lung Cancer 
ROZLYTREK is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. 

2 DOSAGE AND ADMINISTRATION 
2.1 Patient Selection 
Select patients for the treatment of metastatic NSCLC with ROZLYTREK based on the presence of ROS1 rearrangement(s) in tumor specimens (see Clinical Studies [14.1]). An FDA-approved test for detection of ROS1 rearrangement(s) in NSCLC for selecting patients for treatment with ROZLYTREK is not available. 

2.2 Recommended Dosage for ROS1-Positive Non-Small Cell Lung Cancer 
The recommended dosage of ROZLYTREK is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity. 

6 ADVERSE REACTIONS 
6.1 Clinical Trial Experience 
(...)

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

14 CLINICAL STUDIES 
14.1 ROS1-Positive Non-Small Cell Lung Cancer 
The efficacy of ROZLYTREK was evaluated in a pooled subgroup of patients with ROS1-positive metastatic NSCLC who received ROZLYTREK at various dosages and schedules (96% received ROZLYTREK 600 mg orally once daily) and were enrolled in one of three multicenter, single-arm, open-label clinical trials: ALKA, STARTK-R1 (NCT02097810) and STARTK-R2 (NCT02568267). To be included in this pooled subgroup, patients were required to have histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG performance status ≥2, measurable disease per RECIST v1.1, ≥12 months of follow-up from first post-treatment tumor assessment, and no prior therapy with a ROS1 inhibitor. Identification of ROS1 gene fusion in tumor specimens was prospectively determined in local laboratories using either a fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS) laboratory-developed test. All patients were assessed for CNS lesions at baseline. (…)

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 (3.9%); never smoked (57%); and ECOG performance status 0 or 1 (88%). Ninety-four 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 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)

212725, 08/15/2019 
Enterceptinib (1) | Oncology | NTRK | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE 
1.2 NTRK Gene Fusion-Positive Solid Tumors 
ROZLYTREK is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

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

This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
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2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
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.

2.3 Recommended Dosage for NTRK Gene Fusion-Positive Solid Tumors
Adults
The recommended dosage of ROZLYTREK in adults is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity.

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
(…)

8.4 Pediatric Use
The safety and effectiveness of ROZLYTREK in pediatric patients aged 12 years and older with solid tumors that have an NTRK gene fusion have been established. The effectiveness of ROZLYTREK in adolescent patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumors harboring an NTRK gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacometric data in adolescents enrolled in STARTRK-NG. (…)

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

14 CLINICAL STUDIES
14.2 NTRK Gene Fusion-Positive Solid Tumors
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 (NC102097810) and STARTRK-2 (NC102968267). 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 600 mg orally once daily) until unacceptable toxicity or disease progression. Identification of positive NTRK gene fusion status was prospectively determined in local laboratories or a central laboratory using various nucleic acid-based tests. (…)

(…)

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 (46%). Ninety-six percent of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), or systemic therapy (n = 48). 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)

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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 who 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 (NCT02365597) 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, G337C, Y373C) or FGFR2 gene fusions (FGFR3-TCAC, FGFR3-BAP1, 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 RQK RT-PCR Kit, which is the FDA-approved test for selection of patients with mUC for BALVERSA. (See Table 5) (…)

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)].

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 (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, G337C, Y373C) or FGFR2 gene fusions (FGFR3-TCAC, FGFR3-BAP1, 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 RQK RT-PCR Kit, which is the FDA-approved test for selection of patients with mUC for BALVERSA. (See Table 5) (…)

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 : -), presence of visceral disease (82%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (…)

14 CLINICAL STUDIES
14.1 Metastatic Breast Cancer
(…) 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 : -), presence of visceral disease (82%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (…)

1 INDICATIONS AND USAGE
1.1 Non-Small Cell Lung Cancer (NSCLC)
TARCEVA® is indicated for:
• 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)].

Limitations of use:
• 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)].

* Therapeutic areas do not necessarily reflect the CDER review division.
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<th>Biomarker†</th>
<th>Labeling Sections</th>
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<td>Esomeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions</td>
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<td>Psychiatry</td>
<td>CYP2D6</td>
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<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>Drug Interactions, Clinical Pharmacology</td>
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#### 2 DOSAGE AND ADMINISTRATION

2.1 Selection of Patients with Metastatic NSCLC

Select patients for the treatment of metastatic NSCLC with TARCEVA based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor or plasma specimens [See Clinical Studies (14.1, 14.2)]. If these mutations are not detected in a plasma specimen, test tumor tissue if available. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

#### 6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Non-Small Cell Lung Cancer

First-Line Treatment of Patients with EGFR Mutations

The most frequent (>30%) adverse reactions in TARCEVA-treated patients were diarrhea, asthenia, cough, dyspnea, and decreased appetite. In TARCEVA-treated patients the median time to onset of rash was 15 days and the median time to onset of diarrhoea was 32 days. (…)

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) – First-Line Treatment of Patients with EGFR Mutations

Study 1

The safety and efficacy of TARCEVA as monotherapy for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or exon 21 (L858R) substitution mutations was demonstrated in Study 1, a randomized, open-label, clinical trial conducted in Europe. One hundred seventy-four (174) White patients were randomized 1:1 to receive erlotinib 150 mg once daily until disease progression (n = 88) or four cycles of a standard platinum-based doublet chemotherapy (n = 88). Standard chemotherapy regimens were cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. Randomization was stratified by EGFR mutation (exon 19 deletion or exon 21 (L858R) substitution) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1 vs. 2). EGFR mutation status for screening and enrollment of patients was determined by a clinical trials assay (CTA). Tumor samples from 134 patients (69 patients from the erlotinib arm and 65 patients from the chemotherapy arm) were tested retrospectively by the FDA-approved companion diagnostic, cobas® EGFR Mutation Test. (…)

7 DRUG INTERACTIONS

7.19 Drugs Metabolized by Cytochrome P4502D6

In vitro studies did not reveal an inhibitory effect of esolapram 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 esolapram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on esolapram metabolism. (…)

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<td>Estradiol and Progesterone (1)</td>
<td>Oncology</td>
<td>PROC</td>
<td>Contraindications</td>
<td>BIJUVA (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>Estradiol and Progesterone (2)</td>
<td>Oncology</td>
<td>PROS1</td>
<td>Contraindications</td>
<td>BIJUVA (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>210132, 10/28/2018</td>
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<td>SERPINC1 (Antithrombin III)</td>
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<td>BIJUVA (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>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. 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>
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<tr>
<td>022334, 02/13/2020</td>
<td>Everolimus (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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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<tr>
<td>022334, 02/13/2020</td>
<td>Everolimus (2)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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 DISPERZ 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, HER 2-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Table 20 and Figure 1) (…) 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 (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. 2 DOSAGE AND ADMINISTRATION 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 5.8 Geriatric Patients In the randomized hormone receptor-positive, HER2-negative breast cancer study (BOLORE-2), the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients &lt; 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients &lt; 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [see Dosage and Administration (2.9), 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 = 488) vs. placebo in combination with exemestane (n = 239) was evaluated in a randomized, controlled trial (BOLORE-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. (See Tables 6 and 7) (…) 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 DISPERZ in pediatric patients have not been established in: - Hormone receptor-positive, HER2-negative breast cancer (…) 8.5 Geriatric Use In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness were observed between elderly and younger patients. (…) 12 CLINICAL PHARMACOLOGY</td>
</tr>
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</table>

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| 02/11/2021, 761181                    | Evinacumab-dgnb (1) | Endocrinology | LDLR       | Clinical Studies | 12.3 Pharmacokinetics

(…)(…) The concomitant administration 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, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Table 20 and Figure 1) (…) |

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Safety data are based on pooled results from two randomized, double-blind, placebo-controlled trials that included 81 patients treated with EKVEEZA. The mean age of EKVEEZA-treated patients was 48 years (range: 15 to 75 years), 52% were women, 5% were Hispanic, 82% were White, 7% Asian, 3% Black, and 9% Other. Forty-four (54%) EKVEEZA-treated patients had HoFH. Patients received EKVEEZA as add-on therapy to other lipid-lowering therapies, including maximally tolerated statin, ezetimibe, PCSK9 inhibitors, lomitapide, and apheresis. (…) |

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of EKVEEZA as an adjunct to other LDL-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 12 years and older. Use of EKVEEZA for this indication is supported by evidence from adequate and well-controlled trials with additional efficacy and safety data in pediatric patients aged 12 years and older [see Adverse Reactions (6.1) and Clinical Studies (14)]. The safety and effectiveness of EKVEEZA have not been established in patients with HoFH who are younger than 12 years old. |

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Administration of evinacumab-dgnb to HoFH patients resulted in reductions in LDL-C, total cholesterol (TC), HDL-C, apolipoprotein B and TG [see Clinical Studies (14)]. |

12.3 Pharmacokinetics

The pharmacokinetic parameters described in this section are presented following administration of evinacumab-dgnb 15 mg/kg intravenously every 4 weeks, unless otherwise specified. Steady-state is reached after 4 doses, and the accumulation ratio is 2. According to population pharmacokinetic modeling, the mean (standard deviation) steady-state trough concentration is 241 (96.5) mg/L whereas the mean (standard deviation) Cmax at the end of infusion is 689 (157) mg/L. Due to non-linear clearance, a 4.3-fold increase in area under the concentration-time curve at steady-state (AUCss) for a 3.3-fold increase in evinacumab-dgnb dose up to 15 mg/kg IV every 4 weeks was predicted in patients with HoFH. |

Specific Populations

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020753, 05/18/2018
Exemestane
Oncology
ESR, PGR
(Hormone Receptor)
Indications and Usage, Dosage and Administration, Clinical Studies

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.

14 CLINICAL STUDIES
14.1 Adjuvant Treatment in Early Breast Cancer
The Intergroup Exemestane Study 031 (IES) was a randomized, double-blind, multicenter, multinational study comparing exemestane (25 mg/day) vs. tamoxifen (20 or 30 mg/day) in postmenopausal women with early breast cancer. (See Table 5) (…)

107139, 12/20/2019
Fam-Trastuzumab Deruxtecan-nxki
Oncology
ERBB2
(HER2)
Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies

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 anti-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

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<td>Urology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>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 untreated or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. (…)</td>
</tr>
</tbody>
</table>

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…) The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with untreated or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study D85201-A-J101 (NCT02556490). ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31). (…) |

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use
Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall differences in efficacy were observed between patients 65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (53%) as compared to younger patients (42%). |

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, untreated and/or metastatic breast cancer who received two or one prior anti-HER2 therapies. Patients were excluded for a history of treated I LD or current I LD 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. (…) |

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 clarithromycin. 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 CYP3D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYPD6 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 CYPD6 inhibitors was not tested clinically. In poor metabolizers for CYPD6, representing a maximum CYPD6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- to 2-fold, respectively. No dosing adjustments are recommended in the presence of CYPD6 inhibitors. |

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<td>Clinical Pharmacology</td>
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<td>Dermatology</td>
<td>DPYD</td>
<td>Contraindications, Warnings</td>
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</table>

**Labeling Text**

Metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. In a separate study coadministering fesoterodine with ketoconazole 200 mg once a day for 5 days, the Cmax and AUC values of the active metabolite of fesoterodine were increased 2.2-fold in CYP2D6 extensive metabolizers and 1.5- and 1.9-fold, respectively, in CYP2D6 poor metabolizers. Cmax and AUC were 3.4- and 4.2 fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. There is no clinically relevant effect of moderate CYP3A4 inhibitors on the pharmacokinetics of fesoterodine. (…) CYP2D6 inhibitors. The interaction with CYP2D6 inhibitors was not studied. In poor metabolizers for CYP2D6, with a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. (see Drug Interactions (7.4)).

**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 flibanserin 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 fribanserin 100 mg once daily decreased 23% and 18%, compared to exposures among 8 extensive metabolizers of CYP2C9.

**CYP2C19 Poor Metabolizers**

In a pharmacogenomic study of 100 mg ADDYI in subjects who were poor or extensive CYP2C19 metabolizers, syncope occurred in 1/9 (11%) subjects who were CYP2C19 poor metabolizers (this subject had a 3.2 fold higher fribanserin exposure compared to CYP2C19 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C19 extensive metabolizers (see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)).

**8 USE IN SPECIFIC POPULATIONS**

**8.7 CYP2C19 Poor Metabolizers**

CYP2C19 poor metabolizers had increased fribanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer (see Adverse Reactions (6.1) and Clinical Pharmacology (12.5)). Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.

**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 fribanserin 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 fribanserin 100 mg once daily increased 1.5-fold (1.1–2.1) and 1.3-fold (0.9–2.1), compared to exposures among 8 extensive metabolizers of CYP2C9. Fribanserin half-life was increased from 8.7 hours in the extensive metabolizers of CYP2C19 to 13.5 hours in the poor metabolizers of CYP2C19 (see Adverse Reactions (6.1) and Use in Specific Populations (8.7)).

The frequencies of poor metabolizers of CYP2C19 are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.

**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 fribanserin 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 fribanserin 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.

**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 fribanserin exposure in CYP2D6 poor metabolizers to CYP2D6 extensive metabolizers was conducted in lieu of a drug interaction study with carisoprodol, a strong CYP2D6 inhibitor. In 12 poor metabolizers of CYP2D6, steady state Cmax and AUC of fribanserin 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.

**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. Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.
### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2021**

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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>
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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>012209, 07/29/2016</td>
<td>Fluorouracil (2)</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td></td>
<td>Patient Counseling Information</td>
<td>5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity</td>
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<td>Based on postmarketing reports, patients with certain homozgyous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil. 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.</td>
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<tr>
<td>020101, 01/30/2009</td>
<td>Fluoxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions, Clinical Pharmacology</td>
<td>PRECAUTIONS:</td>
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<td></td>
<td>Drug interactions</td>
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<td>Drugs metabolized by CYP2D6: Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarhythmic (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).</td>
</tr>
<tr>
<td>018766, 05/09/2016</td>
<td>Flurbiprofen</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td></td>
<td>12.3 Pharmacokinetics</td>
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<td>Poor Metabolizers of CYP2C9 Substrates</td>
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<td>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.</td>
</tr>
<tr>
<td>018554, 07/23/2001</td>
<td>Flutamide</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Warnings</td>
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<td>Aniline Toxicity:</td>
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<td>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.</td>
</tr>
<tr>
<td>022007, 05/20/2019</td>
<td>Formoterol (1)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Metabolism</td>
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</tbody>
</table>

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<th>Labeling Text‡</th>
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<td>02/2007, 05/26/2019</td>
<td>Fosdenopterin</td>
<td>Neurology</td>
<td>MOCS1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.</td>
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<tr>
<td>02/20/2019, 214018</td>
<td>Formoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.</td>
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<td>Phenytoin (1)</td>
<td>Neurology</td>
<td>CYP2C9</td>
<td>Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td></td>
</tr>
</tbody>
</table>

5 WARNINGS AND PRECAUTIONS

5.4 Serious Dermatologic Reactions
CEREBYX can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin (the active metabolite of CEREBYX)-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.5)]. The onset of symptoms is usually within 28 days, but can occur up to 3 days after discontinuation of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding CEREBYX as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers. Should CEREBYX be utilized for CYP2C9*3 carriers, consider starting at the lower end of the dosage range [see Use in Specific Populations (8.7)].

The use of HLA-B*1502 or CYP2C9 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

8 USE IN SPECIFIC POPULATIONS

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

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics
CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate (e.g., *1/*3, *2/*2) or poor metabolism (e.g., *2/*3, *3/*3) have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also result in decreased clearance of phenytoin (e.g., *5, *6, *8, *11). The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2-3% in the White population, 0.5-4% in the Asian population, and <1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-30% in the Asian population (see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)).

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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<td>Fluvoxamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS</td>
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<td></td>
<td>7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes</td>
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<td>(…) 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 &quot;poor metabolizers&quot; (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 &quot;extensive metabolizers&quot; (EM): mean Cmax, AUC, and half-life were increased by 52%, 200%, and 69%, 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 medications, comorbidities, and the level of dermatologic monitoring have not been studied.</td>
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<tr>
<td>Duloxetine</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>Monotherapy</td>
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<td>FASLODEX is indicated for the treatment of:</td>
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<td>- 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</td>
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<td>- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.</td>
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<td>Combination Therapy</td>
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<td>FASLODEX is intended for the treatment of:</td>
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<td>- 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.</td>
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<td>- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.</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>Combination Therapy</td>
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<td>Combination Therapy with Palbociclib (PALOMA-3)</td>
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<td>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. (…)</td>
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<td>Combination Therapy with Abemaciclib (MONARCH 2)</td>
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<td>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. (…)</td>
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<td>Combination Therapy with Ribociclib (MONALEESA-3)</td>
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<td>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. (…)</td>
</tr>
</tbody>
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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. (…)

Combination Therapy

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

FASLODEX 500 mg in Combination with Palbociclib 125 mg (PALOMA-3)

PALOMA-3 (NCT-1942135) was an international, randomized, double-blind, parallel group, multi-center study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with HRPositive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…)

FASLODEX 500 mg in Combination with Abemaciclib 150 mg (MONARCH 2)

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multi-center study conducted in women with HR-positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy treated with FASLODEX plus abemaciclib versus FASLODEX plus placebo. (…)

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy.

FASLODEX 500 mg in Combination with Ribociclib 600 mg (MONALEESA-3)

MONALEESA-3 (NCT02422615) was a randomized, double-blind, placebo-controlled study of FASLODEX plus ribociclib versus FASLODEX plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)

Comparison of FASLODEX 500 mg and Anastrozole 1 mg (FALCON)

The safety of FASLODEX 500 mg versus anastrozole 1 mg was evaluated in FALCON. The data described below reflect exposure to FASLODEX in 228 out of 460 patients with HR-positive advanced breast cancer in postmenopausal women not previously treated with endocrine therapy who received at least one (1) dose of treatment in FALCON. (…)

Combination Therapy

Comparison Therapy with Palbociclib (PALOMA-3)

The safety of FASLODEX 500 mg plus palbociclib in 430 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 palbociclib or placebo in PALOMA-3. (…)

Combination Therapy with Ribociclib (MONALEESA-3)

The safety of FASLODEX 500 mg plus ribociclib in 604 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus ribociclib or placebo in MONALEESA-3. (…)

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor.
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| 021169, 02/14/2017                     | Galantamine | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  
Metabolism and Elimination  
Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 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 3H-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 96% 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 RAZADYNE® ER extended-release capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER extended-release capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. (…) CYP2D6 Poor Metabolizers Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as ‘poor metabolizers’. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% 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. |
| 206995, 08/22/2018                     | Gefitinib (1) | Oncology | EGFR | Indications and Usage, Dosage, Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations 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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**Last Updated: 06/2021**

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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</table>
| 206965, 06/22/2018                     | Gefitinib (2) | Oncology | CYP2D6 | Clinical Pharmacology | 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 diagnosis of 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 87 patients were tested retrospectively using the therascreen® EGFR RQG PCR 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 (45%), WHO PS 2 (7%), and adenocarcinoma histology (97%). Sixty patients had exon 19 deletions (65%), 29 patients had L858R substitution (31%), while 10 patients each had tumors harboring L861Q or G719X substitution mutation. The median duration of treatment was 8.0 months. (See Table 3) The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation with duration of response of at least 2.8 months and 5.6 months, respectively. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response with duration of response of at least 2.8 months. Study 2 The results of Study 1 were supported by an exploratory analysis of a subset of a randomized, multicenter, open-label trial (Study 2) conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients were randomized (1:1) to receive IRESSA 250 mg orally once daily or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and objective response rate (ORR) as assessed by BICR. The subset population consisted of 186 of 1217 patients (15%) determined to be EGFR positive by the same clinical trial assay as used in Study 1 and had radiographic scans available for a retrospective assessment by BICR. In this subset, there were 88 IRESSA-treated patients and 98 carboplatin/paclitaxel-treated patients. (…)

| 761060, 06/16/2020                     | Gemtuzumab Ozogamicin | Oncology | CD33 | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Newly-Diagnosed CD33-positive Acute Myeloid Leukemia (AML)  
MYLOTARG is indicated for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults and pediatric patients 1 month and older.  
1.2 Relapsed or Refractory CD33-positive AML  
MYLOTARG is indicated for the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and pediatric patients 2 years and older.  
2 DOSAGE AND ADMINISTRATION  
2.2 Recommended Dosage  
Newly-Diagnosed De Novo CD33-positive AML (Combination Regimen)  
Adults  
The recommended dose of MYLOTARG in adults is 3 mg/m². A treatment course including MYLOTARG in combination therapy for adults with newly-diagnosed de novo CD33-positive AML consists of 1 induction cycle and 2 consolidation cycles (see Clinical Studies (14.1)). (…)  
Newly-Diagnosed CD33-positive AML (Single-agent Regimen)  
A treatment course of MYLOTARG as a single agent for adults with newly-diagnosed CD33-positive AML consists of 1 cycle of induction and up to 8 cycles of continuation therapy (see Clinical Studies (14.1)). (…)  
Relapsed or Refractory CD33-positive AML (Single-agent Regimen)  
The recommended dose of MYLOTARG as a single agent for treatment for adults and pediatric patients 2 years and older with relapsed or refractory CD33- positive AML is 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7. Treatment in the relapsed or refractory setting consists of a single course of MYLOTARG (see Clinical Studies (14.2)). (…)  
6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Combination Therapy in Newly-Diagnosed De Novo CD33-positive AML  
The safety of MYLOTARG in first-line combination therapy was evaluated in two prospective clinical trials, Study ALFA-0701 in adults and Study AAML0531 in pediatric patients. (…)

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<td>Monotherapy for Newly-Diagnosed CD33-positive AML</td>
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<td>The safety evaluation of MYLOTARG (6 mg/m² then 3 mg/m² , with 7 days between the doses) as monotherapy is based on a randomized, open-label, Phase 3 trial of MYLOTARG (N=118) versus best supportive care (BSC) (N=119) in patients with previously untreated AML who were considered ineligible for intensive chemotherapy in Study AML-19 [see Clinical Studies (14.1)]. (…)</td>
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<td>The adverse reactions described in this section reflect exposure to MYLOTARG 3 mg/m² on Days 1, 4 and 7 as monotherapy in 57 patients with relapsed AML treated on MyloFrance-1 [see Clinical Studies (14.1)]. All 57 (100%) patients received the 3 planned doses of MYLOTARG. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Newly-Diagnosed CD33-positive AML Study ALFA-0701</td>
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<td>Study AML-19</td>
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<td>(…) 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; 15% had CD33 expression less than 20%. (…)</td>
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<td>14.2 Relapsed or refractory CD33-positive AML Study MyloFrance-1</td>
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<td>The efficacy of MYLOTARG as a single agent was evaluated in MyloFrance-1 a phase 2, single-arm, open-label study in adults with CD33-positive AML in first relapse. (…)</td>
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<tr>
<td>211349, 05/29/2019</td>
<td>Gilteritinib</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.1 Relapsed or Refractory Acute Myeloid Leukemia</td>
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<td>XOSPATA is indicated for the treatment of patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection</td>
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<td>Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>The efficacy of XOSPATA was assessed in the ADMIRAL trial (NCT02421939), which included 138 adult patients with relapsed or refractory AML having a FLT3-ITD, D835, or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. (See Table 4) (…)</td>
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<td>(…) For patients who achieved a CR/CRI, the median time to first response was 3.6 months (range: 0.9 to 9.6 months). The CR/CRI rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 3 of 21 in patients with FLT3-TKD only. (See Table 6) (…)</td>
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<td>(…) In the final analysis, the CR/CRI rate in the gilteritinib arm was 22.6% (55/243) and the DOR was 7.4 months (range, &lt;0.1 to 23.1). For patients who achieved a CR/CRI, the median time to first response was 2 months (range, 0.9 to 9.6 months). The CR/CRI rate was 49 of 215 in patients with FLT3-ITD only, 3 of 7 in patients with FLT3-ITD/TKD and 3 of 21 in patients with FLT3-TKD only. (…)</td>
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<td>212194, 11/20/2019</td>
<td>Givosiran</td>
<td>Gastroenterology</td>
<td>CPOX, HMBS, PPOX (Acute Hepatic Porphyria)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>The efficacy of GIVLAARI in patients with acute hepatic porphyria was evaluated in the ENVISION trial (NCT03338816), a randomized, double-blind, placebo-controlled, multinational study. ENVISION enrolled 94 patients with acute hepatic porphyria (AHP) (89 patients with AIP, 2 patients with variegate porphyria [VP], 1 patient with hereditary coproporphyria [HCP], and 2 patients with no identified mutation). (…)</td>
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<td>Endocrinology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.3 Hemolytic Anemia</td>
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<td>Sulfonlureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonlurea alternatives. There are also postmarketing reports of hemolytic anemia in patients receiving AMARYL who did not have known G6PD deficiency [see Adverse Reactions (6.2)].</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.2 Postmarketing Experience</td>
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<td>Precautions</td>
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<td>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.</td>
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<td>G6PD</td>
<td>Precautions</td>
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<td>Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonlurea agents can lead to hemolytic anemia. Because GLYNASE PresTab 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>
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<td>DMD</td>
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<td>Oncology</td>
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<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
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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) (...]

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<tr>
<td>022192, 05/03/2021</td>
<td>Hydrochloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.6 Hemolytic Anemia Associated with G6PD Deficiency Hemolysis has been reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor for hemolytic anemia as this can occur, particularly in association with other drugs that cause hemolysis.</td>
</tr>
<tr>
<td>205552, 04/21/2020</td>
<td>Ibrutinib (1)</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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)].</td>
</tr>
<tr>
<td>205552, 04/21/2020</td>
<td>Ibrutinib (2)</td>
<td>Oncology</td>
<td>Chromosome 11q</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma RESONATE (…) Thirty-two percent of patients had 17p deletion. (…) RESONATE included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for del 17p CLL/SLL are shown in Table 22. (See Table 22) 63-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. iLLUMINATE The iLLUMINATE study (a multi-center study of ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab) (NCT02264574) was conducted in patients with treatment-naive CLL or SLL. Patients were 65 years of age or older or &lt; 65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance &lt; 70 mL/min, or presence of del17p/TP53 mutation. (…) The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with CLL/SLL with high risk factors (del17p/TP53 mutation [18%], del 11q [15%], or unmutated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy included: lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%). (…) In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].</td>
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<tr>
<td>205552, 04/21/2020</td>
<td>Ibrutinib (3)</td>
<td>Oncology</td>
<td>MYD88</td>
<td>Clinical Studies</td>
<td>14.3 Waldenström’s Macroglobulinemia INNOVATE (…) At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status. (…)</td>
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<tr>
<td>022192, 02/23/2017</td>
<td>Iloperidone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration</td>
<td>2 DOSAGE AND ADMINISTRATION 2.2 Dosage in Special Populations</td>
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| **021588, 08/21/2018**                | **Imatinib (1)** | **Oncology** | **KIT** | **Indications and Usage, Dosage and Administration, Clinical Studies** | **Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6**  
**FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 [see Clinical Pharmacology (12.3)].** |

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: Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2- to 3-fold, and decreased the AUC of its metabolite 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, 28, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3-4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4.

14.5 Myelodysplastic/Myloloproliferative Diseases

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

14.6 Aggressive Systemic Mastocytosis

Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I) and four patients had a D816V c-Kit mutation (not associated with Abl, Kit or PDGFR protein tyrosine kinases. (…)

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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 | <p>…</p><p>Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.</p><p>14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia</p><p>One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abi, Kit or PDGFR protein tyrosine kinases. (<p>)</p><p>14.8 Dermatofibrosarcoma Protuberans</p><p>(…) An open-label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients with life-threatening diseases associated with Abi, Kit or PDGFR protein tyrosine kinases. (<p>)</p><p>14.9 Gastrointestinal Stromal Tumors</p><p>(…) One open-label, multinational Phase 2 study was conducted with patients with Kit (CD117) positive unresectable or metastatic malignant GIST. (<p>)</p><p>Adjuvant Treatment of GIST</p><p>In the adjuvant setting, Gleevec was investigated in a multicenter, double-blind, placebo-controlled, randomized trial involving 713 patients (Study 1). Patients were randomized one to one to Gleevec at 400 mg/day or matching placebo for 12 months. The ages of these patients ranged from 18 to 91 years. Patients were included who had a histologic diagnosis of primary GIST, expressing Kit protein by immunohistochemistry and a tumor size greater than or equal to 3 cm in maximum dimension with complete gross resection of primary GIST within 14 to 70 days prior to registration. (<p>)</p><p>(…) A second randomized, multicenter, open-label, phase 3 trial in the adjuvant setting (Study 2) compared 12 months of Gleevec treatment to 36 months of Gleevec treatment at 400 mg/day in adult patients with Kit (CD117) positive GIST after surgical resection with one of the following: tumor diameter greater than 5 cm and mitotic count greater than 5/50 high power fields (HPF), or tumor diameter greater than 10 cm and any mitotic count, or tumor of any size with mitotic count greater than 10/50 HPF, or tumors ruptured into the peritoneal cavity. (<p>)</p><p>1 INDICATIONS AND USAGE</p><p>1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)</p><p>Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. (<p>)</p><p>1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy</p><p>Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. (<p>)</p><p>1.3 Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)</p><p>Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia. (<p>)</p><p>1.4 Pediatric patients with Ph+ Acute Lymphoblastic Leukemia (ALL)</p><p>Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy. (<p>)</p><p>2 DOSAGE AND ADMINISTRATION</p><p>2.2 Adult Patients with Ph+ CML CP, AP, or BC</p><p>The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML-CP, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response. (<p>)</p><p>2.3 Pediatric Patients with Ph+ CML CP</p><p>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—two 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. (<p>)</p><p>2.4 Adult Patients with Ph+ ALL</p><p>The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL. (<p>)</p><p>2.5 Pediatric Patients with Ph+ ALL</p><p>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. (<p>)</p><p>2.14 Dose Adjustment for Hematologic Adverse Reactions</p><p>Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (<p>)</p><p>5 WARNINGS AND PRECAUTIONS</p><p>5.1 Fluid Retention and Edema</p><p>(…) In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Gleevec and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Gleevec and in 3.9% of patients receiving nilotinib 300 mg bid. (<p>)</p><p>5.3 Congestive Heart Failure and Left Ventricular Dysfunction</p><p>(…) In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. In another randomized trial with newly diagnosed Ph+ CML patients in chronic phase that compared Gleevec and nilotinib, cardiac failure was observed in 1.1% of patient in the Gleevec arm and 2.2% of patients in the nilotinib 300 mg bid arm and severe (Grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. (<p>)</p><p>5.5 Hemorrhage</p><p>* Therapeutic areas do not necessarily reflect the CDER review division.† Represented 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. 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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 16 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 at 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 edemata. These edemata 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

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<td>Oncology</td>
<td>PDGFRB</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML, recurrent after stem cell transplant or resistant to interferon-alpha therapy. (…). In the second study, 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.</td>
</tr>
<tr>
<td>02/1568, 08/21/2018</td>
<td>Imatinib (4)</td>
<td>Oncology</td>
<td>FIP1L1-PDGFR-RA</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>One representative biomarker is 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 “Non-specific” 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.</td>
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| 017090, 07/28/2014                     | Imipramine    | Psychiatry       | CYP2D6     | 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). |
| 022383, 05/29/2019                     | Indacaterol   | Pulmonary        | UGT1A1     | Clinical Pharmacology  
12 CLINICAL PHARMACOLOGY  
12.4 Pharmacogenomics  
The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as “08” and the (TA)6, (TA)7 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7], (TA)7 genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure. |
| 761142, 06/11/2020                     | Nebulizerab-cdon | Neurology   | AQP4       | 1 INDICATIONS AND USAGE  
UPLIZNA is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. |
|                                         | Fingratinib   | Oncology        | FGF2       | 1 INDICATIONS AND USAGE  
TRUSELTIQ is indicated for the treatment of adults with previously treated, unselectable 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 (2.11)].  
This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).  
2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Select patients for the treatment of unselectable locally advanced or metastatic cholangiocarcinoma with TRUSELTIQ based on the presence of an FGFR2 fusion or rearrangement, as detected by an FDA-approved test [see Clinical Studies (14.1)]. |

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<td>Adverse Reactions, Clinical Pharmacology</td>
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<td>(…) Baseline disease characteristics were largely similar in TEGSEDI-treated patients and patients in the placebo control group. Sixty-seven percent of patients were in Stage 1 of the disease at baseline, and 33% in Stage 2. Fifty-two percent of patients had Val30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different point mutations. (…)</td>
<td>6 ADVERSE REACTIONS</td>
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<td>761040, 08/17/2017</td>
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<td>14.1 Unresectable or Metastatic Melanoma</td>
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<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
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<td>1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.4)]. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>6.1 Clinical Trials Experience</td>
<td>The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (&gt;1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma; and to YERVOY 1 mg/kg, administered in combination with nivolumab, in two trials: CHECKMATE214 (NCT02231749), a randomized trial in previously untreated patients with advanced renal cell carcinoma, and CHECKMATE-142 (NCT02606188), an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer. (…) Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, non-randomized, multiple parallel-cohort study. In CHECKMATE-142, 119 patients with previously treated MSI-H or dMMR mCRC received YERVOY, in combination with nivolumab, in a single-arm cohort. In another single-arm cohort under CHECKMATE-142, 74 patients with mCRC received nivolumab monotherapy. (See Tables 9 and 10) (…) 8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma or for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY in this age group is supported by evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacokinetic data demonstrating that the exposure at doses of 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of advanced melanoma and MSI-H or dMMR metastatic colorectal cancer are sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients. (…) 14 CLINICAL STUDIES 14.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer CHECKMATE-142 (NCT02606188) was a multicenter, non-randomized, multiple parallel cohort, open-label study conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG PS 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients enrolled in the YERVOY and nivolumab MSI-H mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV every 2 weeks. Patients enrolled in the single-agent nivolumab MSI-H mCRC cohort received nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (See Table 22) (…)</td>
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<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 ($\geq 1\%$) 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/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics)

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 $\geq 1\%$) 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, 1.18) 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-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. (…)

14.6 Metastatic Non-Small Cell Lung Cancer

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

CHECKMATE-221 (NCT02416326) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [IASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. (…)

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression $1\%$. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). (…)

In Part 1a, a total of 793 patients were randomized to receive either YERVOY in combination with nivolumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients 65 years or older and 10% of patients 75 years or older. Baseline ECOG performance status was 0 (34%) or 1 (66%), 50% with PD-L1 $\geq 1\%$, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers. The study demonstrated a statistically significant improvement in OS for PD-L1 $\geq 1\%$ patients randomized to the YERVOY and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 22 and Figure 4. (See Table 24 and Figure 4)

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-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 Stage Association for the Study of Lung Cancer [IASLC]) classification), 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 ($\geq 1\%$ versus $<1\%$ or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. (…)

A total of 719 patients were randomized to receive either YERVOY in combination with nivolumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients 65 years or older and 10% of patients 75 years or older. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (66%), 57% had tumors with PD-L1 expression $1\%$ and 37%

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had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers. (…)

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 <1%.
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| 125377, 11/13/2020                     | Ipilimumab (4) | 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 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. (…)

First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab

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

14 CLINICAL STUDIES

14.6 Metastatic Non-Small Cell Lung Cancer

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

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

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

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. 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  
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6 ADVERSE REACTIONS  
The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIA (>1 mm nodal involvement), IIB, 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. (…)  
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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  
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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-Doublet Chemotherapy  
CHECKMATE-9LA (NCT03215708) 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 17p</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Multiple Myeloma (ICARIA-MM) (…) Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14) and t(14;16) were present in 12%, 8% and 2% of patients, respectively. (…)</td>
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<td>076113, 03/02/2020</td>
<td>Isatuximab-irfc (2)</td>
<td>Oncology</td>
<td>Chromosome 4p;14q</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Multiple Myeloma (ICARIA-MM) (…) Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14) and t(14;16) were present in 12%, 8% and 2% of patients, respectively. (…)</td>
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<td>076113, 03/02/2020</td>
<td>Isatuximab-irfc (3)</td>
<td>Oncology</td>
<td>Chromosome 14q;16q</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Multiple Myeloma (ICARIA-MM) (…) Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14) and t(14;16) were present in 12%, 8% and 2% of patients, respectively. (…)</td>
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**Table of Pharmacogenomic Biomarkers in Drug Labeling**

*Last Updated: 06/2021*

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<th>Labeling Sections</th>
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<td>050705, 02/28/2019</td>
<td>Isoniazid, Pyrazinamide, and Rifampin</td>
<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY (…) Isoniazid is metabolized in the liver mainly by acetylation and dehydrazinization. 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>OVERDOSE Methemoglobinemia Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moiety of isosorbide dinitrate is 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>OVERDOSE Methemoglobinemia Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate 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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<tr>
<td>203188, 04/26/2019</td>
<td>Ivacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.</td>
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<td></td>
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<td>6 ADVERSE REACTIONS</td>
<td>6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The overall safety profile of KALYDECO is based on pooled data from three placebo-controlled clinical trials conducted in 353 patients 6 years of age and older with CF who had a G551D mutation in the CFTR gene (Trials 1 and 2) or were homozygous for the F508del mutation (Trial 3). In addition, the following clinical trials have also been conducted [see Clinical Pharmacology (12) and Clinical Studies (14)]: An 8-week, crossover design trial (Trial 4) involving 39 patients between the ages of 6 and 57 years with a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. A 24-week, placebo-controlled trial (Trial 5) involving 69 patients between the ages of 6 and 68 years with an R117H mutation in the CFTR gene. A 24-week, open-label trial (Trial 6) in 34 patients 2 to less than 6 years of age. Patients eligible for Trial 6 were those with the G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. Of 34 enrolled patients, 32 had the G551D mutation and 2 had the S549N mutation. An 8-week, crossover design trial (Trial 7) involving patients between the ages of 12 and 72 years who were homozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO. A cohort of 19 patients aged 12 months to less than 24 months, and a cohort of 11 patients aged 6 months to less than 12 months in a 24-week, open-label clinical trial in patients with CF aged less than 24 months (Trial 8).</td>
</tr>
</tbody>
</table>

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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 ≥8% 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 S117H 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+5→A, 3272→26A→G, 3849+10kbC→T, 711+3A→G and E831X and these are listed in Table 3 below (see also Clinical Studies (14.4)).

The G970R mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor [see Clinical Studies (14.2)]. Ivacaftor also increased chloride transport in cultured human bronchial epithelial (HBE) cells derived from CF patients who carried F508del on one CFTR allele and either G551D or R117H on the second CFTR allele.

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

**12.2 Pharmacodynamics**

**Sweat Chloride Evaluation**

Changes in sweat chloride (a biomarker) response to KALYDECO were evaluated in seven clinical trials [see Clinical Studies (14)]. In a two-part, randomized, double-blind, placebo-controlled, crossover clinical trial in patients with CF who had a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene (Trial 4), the treatment difference in mean change in sweat chloride from baseline through 8 weeks of treatment was -49 mmol/L (95% CI -57, -41). The mean change 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 ages 6 months to less than 24 months administered 25 mg, 50 mg or 75 mg of ivacaftor twice daily (Trial 8), 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 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. (…)


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<td>Ivacaftor and Lumacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>The efficacy and safety of KALYDECO in patients with CF who are homozygous for the F508del mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. Limitations of Use and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)].</td>
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<td>Ivacaftor and Lumacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>The efficacy and safety of KALYDECO in patients with CF who are homozygous for the F508del mutation in the CFTR gene. 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 who are 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 9). (See Table 10) (…)</td>
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<td>Ivacaftor and Tezacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical</td>
<td>SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.</td>
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6 ADVERSE REACTIONS
(...) The safety profile for 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 homozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (see Clinical Pharmacology (12.1) 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: -11.7, -8.8). In Trial 2 (patients heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor), the treatment difference in mean absolute change from baseline in sweat chloride through Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) between SYMDEKO and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo. (…)

14 CLINICAL STUDIES
Dose Ranging:
Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF homozygous for the F508del mutation (18 years of age and older) with a screening ppFEV1 >24. 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 35 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean ppFEV1 change from baseline were observed with tezacaftor alone and with tezacaftor in combination with ivacaftor. (…)

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| 211192, 05/02/2019                     |ivosidenib | Oncology | IDH1 | Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Newly-Diagnosed Acute Myeloid Leukemia  
TIBSOVO is indicated for the treatment of newly-diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)]. |
| 022065, 10/18/2011                    |Ixabepilone (1) | Oncology | ERBB2 (HER2) | Clinical Studies | 14 CLINICAL STUDIES  
Combination Therapy  
(…) Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6 (…)  
Monotherapy  
HER2-positive patients must also have progressed during or after discontinuation of trastuzumab. In this study, the median age was 51 years (range, 30-78), and 79% were White. 5% were 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% (…) |
| 022065, 10/18/2011                    |Ixabepilone (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES  
Combination Therapy  
(…) Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6 (…)  
Monotherapy  
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<td>Lacosamide</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>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%. (…)</td>
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<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Special Populations CYP2C19 Polymorphism 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.</td>
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<td>022059, 12/06/2018</td>
<td>Lapatinib (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Special Populations, Clinical Studies</td>
<td>2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosing HER2-Positive Metastatic Breast Cancer The recommended dose of TYKERB is 1,250 mg given orally once daily on Days 1-21 continuously in combination with capcitabine 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)]. Captopril should be taken with food or within 30 minutes after food. If a day’s dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs. Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)]. 2.2 Dose Modification Guidelines Hepatic Impairment Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range and should be considered. However, there are no clinical data with this dose adjustment in patients with severe hepatic impairment. Concomitant Strong CYP3A4 Inducers The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John’s wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability. (…) 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience HER2-Positive Metastatic Breast Cancer</td>
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</table>
The efficacy and safety of TYKERB in combination with letrozole in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab. (...) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (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. (...) 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 taxane-based chemotherapy plus TYKERB to taxane-based chemotherapy plus trastuzumab as first-line therapy in women with HER2-positive, metastatic breast cancer (N = 652). (...) 14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer The efficacy and safety of TYKERB in combination with letrozole resulted in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PR positive) metastatic breast cancer, who had 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 = 644) or letrozole (2.5 mg once daily) alone (n = 642). Of all patients randomized to treatment, 219 (17%) patients had tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH) 22 or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2- negative and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective was to evaluate and compare progression-free survival (PFS) in the HER2-positive population. Progression-free survival was defined as the interval of time between date of randomization and the earlier date of first documented sign of disease progression or death due to any cause. The baseline demographic and disease characteristics were balanced between the two treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty-four percent (84%) of the patients were white. Approximately 50% of the HER2-positive population had prior adjuvant/neoadjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab. In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (See Table 8 and Figure 3) The efficacy and safety of TYKERB, in combination with an aromatase inhibitor (AI), were confirmed in another randomized Phase 3 trial. Patients enrolled were post-menopausal women who had hormone receptor-positive (HR+) HER2-positive, metastatic breast cancer, which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies. (...) The efficacy of TYKERB in combination with letrozole was evaluated in a randomized, double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PR positive) metastatic breast cancer, who had 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) 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) 22 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. 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(See Table 8 and Figure 3) The efficacy and safety of TYKERB, in combination with an aromatase inhibitor (AI), were confirmed in another randomized Phase 3 trial. Patients enrolled were post-menopausal women who had hormone receptor-positive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies. (...) The study was designed to evaluate a potential benefit in Progression Free Survival (PFS) when double versus single HER2-targeted therapy was administered in combination with an AI (letrozole, exemestane, or anastrozole). The major efficacy outcome measure was PFS based on local radiology/investigator’s assessment comparing TYKERB + trastuzumab + AI versus trastuzumab + AI. (…)
### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2021**

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<th>Therapeutic Area†</th>
<th>Biomarker‡</th>
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<td>022059, 12/06/2018</td>
<td>Lapatinib (3)</td>
<td>Oncology</td>
<td>HLA-DQA1</td>
<td>Clinical Pharmacology</td>
<td>Hepatic Impairment Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (metastatic hormone receptor-positive, HER2-positive breast cancer indication) in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range and should be considered. However, there are no clinical data with this dose adjustment in patients with severe hepatic impairment. Concomitant Strong CYP3A4 inducers The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampentin, phenobarbital, St. John’s wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability.</td>
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<td>Lapatinib (4)</td>
<td>Oncology</td>
<td>HLA-DRB1</td>
<td>Clinical Pharmacology</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (…) Hormone Receptor-Positive, Metastatic Breast Cancer: In a randomized clinical trial of patients (N = 1,286) with hormone receptor-positive, metastatic breast cancer, who had not received chemotherapy for their metastatic disease, patients received letrozole with or without TYKERB. (…) Hormone Receptor-Positive, HER2+ Metastatic Breast Cancer: 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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<tr>
<td>210861, 11/26/2018</td>
<td>Larotrectinib</td>
<td>Oncology</td>
<td>NTRK</td>
<td>Indications and Usage, Dosage and Administration</td>
<td><strong>1 INDICATIONS AND USAGE</strong> 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. (…) <strong>15 CLINICAL STUDIES</strong> 15.1 HER2-Positive Metastatic Breast Cancer (…) 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. (…) 14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PR 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). (…) In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (…) 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 receptorpositive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies. (…)</td>
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* Therapeutic areas do not necessarily reflect the CDER review division.
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<tr>
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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>Select patients for treatment with VITRAKVI based on the presence of a NTRK gene fusion in tumor specimens [see Clinical Studies (14)]. An FDA-approved test for the detection of NTRK gene fusion is not currently available.</td>
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<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trial Experience</td>
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<td>(…) NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Most adults (80%) received VITRAKVI 100 mg orally twice daily and 68% of pediatrics (18 years or younger) received VITRAKVI 100 mg/m² twice daily up to a maximum dose of 100 mg twice daily. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>The efficacy of VITRAKVI was evaluated in pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials: Study LOXO-TRK-14001 (NCT02122913), S consoles (NCT02837687), and NAVIGATE (NCT02676431). (…) Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH). NTRK gene fusions were inferred in three patients with infantile fibrosarcoma who had a documented ETvε translocation identified by FISH. (…) The assessment of efficacy was based on the first 55 patients with solid tumors with an NTRK gene fusion enrolled across the three clinical trials. (…) The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). A total of 50 patients had NTRK gene fusions detected by NGS and 5 patients had NTRK gene fusions detected by FISH. Efficacy results are summarized in Tables 4, 5, and 6.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.2 Clinical Trials in Subjects with Genotype 1 HCV</td>
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<td>Treatment-Naïve Adults without Cirrhosis — ION-2 (Study 0108)</td>
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<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; 19% were Black; 6% were Hispanic or Latino; mean body mass index was 28 kg/m² (range: 18 to 56 kg/m²); 81% 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). (…)</td>
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<td>Treatment-Naïve Adults with or without Cirrhosis — ION-1 (Study 0102)</td>
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<td>(…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 865 treated subjects, the median age was 54 years (range: 18 to 80); 59% of the subjects were male; 85% were White; 12% were Black; 12% were Hispanic or Latino; mean body mass index was 27 kg/m² (range: 18 to 48 kg/m²); 79% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 67% had genotype 1a HCV infection; 70% had non-C/C IL28B alleles (CT or TT); and 16% had cirrhosis. (…)</td>
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<td>Previously-Treated Adults with or without Cirrhosis — ION-2 (Study 0109)</td>
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<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; 9% were Hispanic or Latino; mean body mass index was 26 kg/m² (range: 19 to 50 kg/m²); 89% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 79% had genotype 1a HCV infection; 88% had non-C/C IL28B alleles (CT or TT); and 20% had cirrhosis. Forty-seven percent (47%) of the subjects failed a prior therapy of pegylated interferon and ribavirin. Among these subjects, 49% were relapse/breakthrough and 51% were non-responder. Fifty-three percent (53%) of the subjects failed a prior therapy of pegylated interferon and ribavirin with an HCV protease inhibitor. Among these subjects, 62% were relapse/breakthrough and 38% were non-responder. (See Table 14) (…)</td>
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<td>Previously-Treated Adults with Cirrhosis — SIRIUS (Study 0121)</td>
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<td>(…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomized subjects, the median age was 56 years (range: 23 to 77); 74% of the subjects were male; 81% of the subjects were White; mean body mass index was 27 kg/m² (range: 19 to 47 kg/m²); 63% had genotype 1a HCV infection; 94% had non-C/C IL28B alleles (CT or TT). One subject discontinued therapy while on placebo, and was not included in the efficacy analysis. (…)</td>
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<td>14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1</td>
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<td>(…) Of the 335 treated subjects, the median age was 52 years (range: 26 to 72); 82% of the subjects were male; 61% were White; 34% were Black; mean body mass index was 27 kg/m² (range: 18 to 66 kg/m²); 75% had genotype 1a HCV infection; 2% had genotype 4 infection; 76% had non-C/C IL28B alleles (CT or TT); and 20% had compensated cirrhosis. Fifty-five percent (55%) of the subjects were treatment-experienced. (…)</td>
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<td>(…) SVR12 rates were 94% (63/67) in subjects with cirrhosis and 98% (46/47) in subjects who were previously-treated and had cirrhosis. The relapse rate in the ION-4 trial in Black subjects was 9% (10/115), all of whom were IL28B non-C/C genotype, and none in non-Black subjects (0/220). In the ION-1, ION-2, and ION-3 HCV mono-infection studies, relapse rates were 3% (10/305) in Black subjects and 2% (26/1637) in non-Black subjects. (…)</td>
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| 206947, 02/20/2020                      | Lenvatinib | Oncology | Microsatellite Instability, Mismatch Repair | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Melolodysplastic Syndromes
REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenic abnormality with or without additional cytogenic abnormalities.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Reovaldysplastic Syndromes
A total of 148 patients received at least 1 dose of 10 mg REVLMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. Thrombocytopenia (61.5%, 91/148) and neutropenia (58.8%, 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (46.6%, 72/148), pruritus (41.9%, 62/148), rash (35.8%, 53/148), and fatigue (31.1%, 46/148). Table 8 summarizes the adverse events that were reported in 2% of the REVLMID treated patients in the del 5q MDS clinical study. Table 9 summarizes the most frequently observed Grade 3 and 4 adverse reactions regardless of relationship to treatment with REVLMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient’s underlying disease. (See Tables 9 and 10)

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use
(…) Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 or over, while 33% were age 75 and over. (…) 

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

207988, 12/22/2015 | Lesinurad | Rheumatology | CYP2C9 | Drug Interactions, Clinical Pharmacology | 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)] 

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism

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<td>020726, 04/05/2018</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lesinurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, ZURAMPIC exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with CYP2C9 *2/*2 [N=1], and *5/*5 [N=1] genotype) compared to CYP2C9 extensive metabolizers (i.e., CYP2C9 *1/*1 [N=41] genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9 (see Drug Interactions [7.1]).</td>
</tr>
<tr>
<td>021451, 11/02/2018</td>
<td>Anesthesiology</td>
<td>Non-specific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions</td>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>021451, 11/02/2018</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
<td>12 CLINICAL PHARMA COLOGY</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>021623, 11/02/2018</td>
<td>Lidoine and Tetracaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>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. (…)</td>
</tr>
<tr>
<td>021623, 11/02/2018</td>
<td>Lidoine and Tetracaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>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. (…)</td>
</tr>
<tr>
<td>209229, 05/16/2018</td>
<td>Lofexidine</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Use in Specific Populations</td>
<td>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)).</td>
</tr>
</tbody>
</table>
| 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 Limitations of Use ZOKINVY is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Based upon its mechanism of action, ZOKINVY would not be expected to be effective in these populations. 6 ADVERSE REACTIONS 6.1 Clinical Trial Experience The safety profile of ZOKINVY is based on 128 patient-years of treatment exposure (62 patients with HGPS and 1 patient with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation) and pooled results from two Phase 2 open-label, single-arm trials (n=63; 28 patients from Study 1 and 35 treatment naive 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 * Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.
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| 213969, 11/20/2020 | Lorlatinib (2) | Inborn Errors of Metabolism | ZMPSTE24 | 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 | 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). (…)

| 210868, 03/03/2021 | Lorlatinib (1) | Oncology | ALK | 1 INDICATIONS AND USAGE LORBRENA® is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of metastatic NSCLC with LORBRENA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics. | The safety and effectiveness of LORBRENA for the treatment of ALK-positive NSCLC is based on adequate and well controlled studies in pediatric patients 2 years of age and older [see Clinical Studies (14)].

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<tr>
<td>210868, 03/03/2021</td>
<td>Lorlatinib (2)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trials Experience</td>
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<td>Previously Treated ALK-Positive Metastatic NSCLC</td>
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<td>The data described below reflect exposure to LORBRENA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA 100 mg orally once daily in Study B7461001; a multi-cohort, non-comparative trial [see Clinical Studies (14)]. The median duration of exposure to LORBRENA was 12.5 months (1 day to 56 months) and 52% received LORBRENA for ≤12 months. Patients with asymptomatic CNS metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were eligible. Patients with severe, acute, or chronic psychiatric conditions including suicidal ideation or behavior were excluded. In addition, for patients with ALK-positive metastatic NSCLC, the extent and type of prior treatment was specified for each individual cohort (see Table 8).</td>
</tr>
<tr>
<td>214103, 11/23/2020</td>
<td>Lumasiran</td>
<td>Urology</td>
<td>AGXT</td>
<td>Indications and Usage, 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>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>
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<td>210923, 07/31/2018</td>
<td>Lusutrombopag (1)</td>
<td>Hematology</td>
<td>F2 (Prothrombin)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td></td>
<td>5.1 Thrombotic/Thromboembolic Complications</td>
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<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 hepatobental blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.</td>
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<tr>
<td>210923, 07/31/2018</td>
<td>Lusutrombopag (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>210923, 07/31/2018</td>
<td>Lusutrombopag (3)</td>
<td>Hematology</td>
<td>PROC</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>210923, 07/31/2018</td>
<td>Lusutrombopag (4)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>210923, 07/31/2018</td>
<td>Lusutrombopag (5)</td>
<td>Hematology</td>
<td>SERPINC1</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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<tr>
<td>208700, 05/29/2020</td>
<td>Lutetium Dotatate Lu-177</td>
<td>Oncology</td>
<td>SSTR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>LUTATHERA is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.</td>
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<td></td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trials Experience</td>
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</table>
|                                        |              |                   |            |                   | The data in Warnings and Precautions reflect exposure to LUTATHERA in 111 patients with advanced, progressive midgut neuroendocrine tumors (NETTER-1). Safety data in Warnings and Precautions were also obtained in an additional 22 patients in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor-positive tumors enrolled in ERASMUS [see Warnings and Precautions (R)]. 

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<td>761150, 12/16/2020</td>
<td>Margetuximab-cmkb (3)</td>
<td>Oncology</td>
<td>FCGR2B (CD32B)</td>
<td>Clinical Pharmacology</td>
<td>or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 37 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2) or concurrent chemotherapies (capecitabine, gemcitabine, erilin and vinorelbine). The effect of severe renal impairment (CLR 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
</tr>
<tr>
<td>761150, 12/16/2020</td>
<td>Margetuximab-cmkb (4)</td>
<td>Oncology</td>
<td>FCGR3A (CD16A)</td>
<td>Clinical Pharmacology</td>
<td>or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 37 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or &gt; 2), number of prior therapy lines (≤ 2 or &gt; 2) or concurrent chemotherapies (capecitabine, gemcitabine, erilin and vinorelbine). The effect of severe renal impairment (CLR 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin &gt; 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin &gt;3 ULN and any AST) on margetuximab-cmkb PK is unknown.</td>
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<tr>
<td>010271, 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 medicine dose and 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 phenothiazin), 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>
<tr>
<td>012250, 11/02/2018</td>
<td>Mepivacaine (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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<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…).</td>
</tr>
<tr>
<td>205919, 04/29/2020</td>
<td>Mercaptopurine (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings and Precautions,</td>
<td>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/m^2) 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 leukemias.</td>
</tr>
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<tr>
<td></td>
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<td></td>
<td>Clinical Pharmacology</td>
<td>status and marrow cellularity. Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or reduced episodes of myelosuppression.</td>
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<td>2.1 Dosage in Patients with TPMT and/or NUDT15 Deficiency</td>
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<td>Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or reduced episodes of myelosuppression (see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)).</td>
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<td></td>
<td>Homozygous deficiency in either TPMT or NUDT15</td>
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<td>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.</td>
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<tr>
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<td></td>
<td>Heterozygous deficiency in TPMT and/or NUDT15</td>
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<td>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.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Myelosuppression</td>
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<td>The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leucopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia.</td>
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<td>Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN (see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)).</td>
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<td>Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity.</td>
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<td>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)).</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>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% (1:3000) 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<em>2, TPMT</em>3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in &lt;1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient’s actual TPMT activity (see Dosage and Administration (2.2) and Warnings and Precautions (5.1)).</td>
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<tr>
<td>204630, 05/21/2018</td>
<td>Methylene Blue</td>
<td>Hematology</td>
<td>G6PD</td>
<td>Contraindications, Warnings and Precautions</td>
<td>PROVAYBLUE™ is contraindicated in the following conditions: • Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)]. • Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia [see Warnings and Precautions (5.3, 5.4)].</td>
</tr>
<tr>
<td>017854, 08/29/2017</td>
<td>Metoclopramide (1)</td>
<td>Gastroenterology</td>
<td>CYB5R</td>
<td>Use in Specific Populations</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.8 NADH-Cytochrome b5 Reductase Deficiency Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal [see Overdosage (10)].</td>
</tr>
<tr>
<td>017854, 08/29/2017</td>
<td>Metoclopramide (2)</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Use in Specific Populations, Overdosage</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.8 NADH-Cytochrome b5 Reductase Deficiency Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal [see Overdosage (10)].</td>
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<td>017854, 06/29/2017</td>
<td>Metoclopramide (3)</td>
<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION  2.2 Dosage for Gastroesophageal Reflux Reglan tablets may be administered continuously or intermittently in patients with symptomatic gastroesophageal reflux who fail to respond to conventional therapy: Continuous Dosing The recommended adult dosage of Reglan is 10 to 15 mg four times daily for 4 to 12 weeks. The treatment duration is determined by endoscopic response. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 60 mg. Table 1 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 1) 2.3 Dosage for Acute and Recurrent Diabetic Gastroesophageal Reflux The recommended adult dosage for the treatment of acute and recurrent diabetic gastroesophageal reflux 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)</td>
</tr>
<tr>
<td>019962, 05/06/2014</td>
<td>Metoprolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS  7.2 CYP2D6 Inhibitors Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol. 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Elimination Metabolism: Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monodeethylmetoclopramide, a major oxidative metabolite, is formed primarily by CYP2D6, an enzyme subject to genetic variability [see Dosage and Administration (2.2, 2.3)]. Use in Specific Populations (8.9)</td>
</tr>
<tr>
<td>125390, 05/15/2020</td>
<td>Metreleptin</td>
<td>Endocrinology</td>
<td>LEP</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS  4.1 General Obesity MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency. MYALEPT has not been shown to be effective in treating general obesity, and the development of anti-metreleptin antibodies with neutralizing activity has been reported in obese patients treated with MYALEPT [see Warnings and Precautions (5.1)].</td>
</tr>
<tr>
<td>207997, 03/04/2020</td>
<td>Midostaurin (1)</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>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</td>
</tr>
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<td>207997, 03/04/2020</td>
<td>Migalast</td>
<td>Inborn Errors of Metabolism</td>
<td>GLA</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
</tr>
<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 RYDAPT 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 LeukoSara® CDx FLT3 Mutation Assay, which is an FDA-approved test for selection of patients with AML for RYDAPT 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 onset in 95%. The percentage of patients with FLT3-ITD allelic ratio &lt; 0.7, FLT3-ITD allelic ratio ≥ 0.7, and FLT3-TKD mutations were identical (per randomized FLT3 stratum) on both arms (48%, 30%, and 23%, respectively). (…)</td>
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<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-findings and were evaluable for response. The median age in this group was 64 years (range: 25-82), 64% of patients were male, and nearly all patients (97%) were Caucasian. Among these patients, 36% had prior therapy for SM, and 62% had the KIT D816V mutation detected at baseline. Their median duration of treatment was 11 months (range: &lt; 1 to 68 months), with treatment ongoing in 17%. Efficacy was established on the basis of confirmed complete remission (CR) plus incomplete remission (ICR) by 6 cycles of RYDAPT by modified Valent criteria for ASM and SM-AHN (Table 7). Table 7 shows responses to RYDAPT according to modified Valent criteria. Confirmed major or partial responses occurred in 46 of 73 patients with a documented KIT D816V mutation, 7 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. (…)</td>
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<td>202811, 04/27/2018</td>
<td>Mirabegron</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>The GLA variants which are amenable to treatment with GALAFOLD, based on the in vitro assay data, are shown in Table 2. Inclusion of GLA variants in this table does not reflect interpretation of their clinical significance in Fabry disease. Whether a certain amenable GLA variant in a patient with Fabry disease is disease-causing or not should be determined by the prescribing physician (in consultation with a clinical genetics professional, if needed) prior to treatment initiation. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease). (See Table 2) If a GLA variant does not appear in Table 2, it is either non-amenable (if tested) or has not been tested for in vitro amenability. For further information, please contact Amicus Medical Information at 1-877-4AMICUS or <a href="mailto:medinfousa@amicusrx.com">medinfousa@amicusrx.com</a>.</td>
</tr>
<tr>
<td>020098, 07/20/2018</td>
<td>Mivacurium</td>
<td>Anesthesiology</td>
<td>BCHE</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
<td>WARNINGS Administration MIVACRON is metabolized by plasma cholinesterase and should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.</td>
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<td>020717, 01/15/2015</td>
<td>Nebivolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>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).</td>
</tr>
<tr>
<td>050791, 10/27/2015</td>
<td>Modafinil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>12.3 Pharmacokinetics</td>
<td>Interactions with CNS Active Drugs CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine and desipramine) and selective serotonin reuptake inhibitors that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased. PROVIGIL may cause elevation of the levels of the tricyclics in this subset of patients (see Drug Interactions (7)).</td>
</tr>
<tr>
<td>014214, 11/28/2012</td>
<td>Mycophenolic Acid</td>
<td>Transplantation</td>
<td>HPRT1</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
<td>Mycophenolic Acid is an inosine monophosphate dehydrogenase inhibitor (IMPDH Inhibitor). Mycophenolic should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease including renal failure.</td>
</tr>
<tr>
<td>021742, 11/30/2017</td>
<td>Nalidixic Acid</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>PRECAUTIONS</td>
<td>Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS)</td>
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| 076037, 07/17/2014                     | Nefazodone | Psychiatry | CYP2D6 | Precautions | **PRECAUTIONS**
Cardiovascular-Active Drugs
Digoxin
When nefazodone (200 mg BID) and digoxin (0.2 mg OD) were coadministered for 9 days to healthy male volunteers (n = 18) who were phenotyped as CYP2D6 extensive metabolizers, Cmax, Cmin, and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Digoxin had no effects on the pharmacokinetics of nefazodone and its active metabolites. Because of the narrow therapeutic index of digoxin, caution should be exercised when nefazodone and digoxin are coadministered; plasma level monitoring for digoxin is recommended.

Propranolol
The coadministration of nefazodone (200 mg BID) and propranolol (40 mg BID) for 5.5 days to healthy male volunteers (n = 18), including 3 poor and 15 extensive CYP2D6 metabolizers, resulted in 30% and 14% reductions in Cmax and AUC of propranolol, respectively, and a 14% reduction in Cmax for the metabolite 4-hydroxypropranolol. The kinetics of nefazodone, hydroxynefazodone, and triazolo-dione were not affected by coadministration of propranolol. However, Cmax, Cmin, and AUC of m-chlorophenylpiperazine were increased by 23%, 54%, and 28%, respectively. No change in initial dose of either drug is necessary and dose adjustments should be made on the basis of clinical response.

CYP2D6 isoenzyme
A subset (3% to 10%) of the population has reduced activity of the drug-metabolizing enzyme CYP2D6. Such individuals are referred to commonly as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. The pharmacokinetics of nefazodone and its major metabolites are not altered in these “poor metabolizers.” Plasma concentrations of one minor metabolite (mCPP) are increased in this population; the adjustment of nefazodone dosage is not required when administered to “poor metabolizers.” Nefazodone and its metabolites have been shown in vitro to be extremely weak inhibitors of CYP2D6. Thus, it is unlikely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme. |

| 208051, 02/25/2020                     | Neratinib (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICTIONS AND USAGE
1.1 Extended Adjuvant Treatment of Early-Stage Breast Cancer
NERLYNX as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer, to follow adjuvant trastuzumab based therapy [see Clinical Studies (14.1)].

1.2 Advanced or Metastatic Breast Cancer
NERLYNX in combination with capcitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting [see Clinical Studies (14.2)].

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Extended Adjuvant Treatment of Early Stage Breast Cancer
ExteNET
The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. (…)

Advanced or Metastatic Breast Cancer
NALA
The data described below reflect the safety data of NERLYNX plus capcitabine in NALA, a randomized, multicenter, multinational, open-label, active-controlled study of HER2+ metastatic breast cancer in patients, with or without brain metastases, who have received two or more prior anti-HER2-based regimens in the metastatic setting. (…)

CONTROL
The CONTROL (NCT02400476) study was a multicenter, open-label, multi-cohort trial evaluating patients with early stage HER2-positive breast cancer treated with neratinib 240 mg daily for up to one year receiving loperamide prophylaxis with and without an additional anti-diarrheal treatment. (…)

14 CLINICAL STUDIES
14.1 Extended Adjuvant Treatment of Early Stage Breast Cancer
The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer. A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). (…)

14.2 Advanced or Metastatic Breast Cancer
The safety and efficacy of NERLYNX in combination with capcitabine was studied in NALA (NCT01806572), a randomized, multicenter, open-label clinical trial in patients (N=621) with metastatic HER2 positive breast cancer who had received 2 or more prior anti-HER2 based regimens in the metastatic setting. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment. HER2 positivity was defined as a HER2 immunohistochemistry (IHC) score of 3+ or IHC 2+ with confirmatory in situ hybridization (ISH) positive. Fifty-nine percent of these patients were hormone receptor positive (HR+); 41% were hormone receptor negative (HR-); 69% had received two or more prior anti-HER2 based regimens, 31% had received three or more prior anti-HER2 based regimens, 81% had visceral disease, and 19% had non-visceral disease. Patients with asymptomatic or stable brain metastases were included in NALA trial of NERLYNX after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer. (…)

14.4 Extended Adjuvant Treatment of Early Stage Breast Cancer
(…)
A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). Randomization was stratified by **CLINICAL STUDIES**

| 208051, 02/25/2020                     | Neratinib (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14.1 Extended Adjuvant Treatment of Early Stage Breast Cancer
(…)
A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). Randomization was stratified by **CLINICAL STUDIES**

* 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 of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2021

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| 02/2068, 09/25/2019                    | Nilotinib (1) | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Adult and Pediatric Patients with Newly Diagnosed Ph+ CML-CP
Tasigna (nilotinib) is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Tasigna is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant to or intolerant to prior treatment that included imatinib. Tasigna is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance to or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
Dosage in Adult Patients with Newly Diagnosed Ph+ CML-CP
The recommended dose of Tasigna is 300 mg orally twice daily.

Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
The recommended dose of Tasigna is 400 mg orally twice daily.

Dosage in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP
The recommended dose of Tasigna for pediatric patients is 230 mg/m² orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

2.2 Discontinuation of treatment after a sustained molecular response (MR4.5) on Tasigna
Patient Selection
Eligibility for Discontinuation of Treatment
Ph+ CML-CP patients with typical BCR-ABL transcripts who have been taking Tasigna for a minimum of 3 years and have achieved a sustained molecular response (MR4.5, corresponding to ≤ BCR-ABL/ABL ≤ 0.0032% IS) may be eligible for treatment discontinuation [see Clinical Studies (14.3, 14.4)]. Information on FDA authorized tests for the detection and quantitation of BCR-ABL transcripts to determine eligibility for treatment discontinuation is available at http://www.fda.gov/CompanionDiagnostics.

Patients with typical BCR-ABL transcripts (i.e., 13a2/b2a2 or e14a2/b3a2) who achieve the sustained MR4.5 criteria are eligible for discontinuation of Tasigna treatment. Patients must continue to be monitored for possible loss of molecular remission after treatment discontinuation. Use the same FDA authorized test to consistently monitor molecular response levels while on and off treatment. Consider discontinuation of treatment in patients with newly diagnosed Ph+ CML-CP who have:
• been treated with Tasigna for at least 3 years
• maintained a molecular response of at least MR4.0 (corresponding to ≤ BCR-ABL/ABL ≤ 0.01% IS) for one year prior to discontinuation of therapy
• achieved an MR4.5 for the last assessment taken immediately prior to discontinuation of therapy
• been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
• no history of accelerated phase or blast crisis
• no history of prior attempts of treatment-free remission discontinuation that resulted in relapse

Consider discontinuation of treatment in patients with Ph+ CML-CP that are resistant or intolerant to treatment with imatinib who have achieved a sustained molecular response (MR4.5) on Tasigna who have:
• been treated with Tasigna for a minimum of 3 years
• been treated with imatinib only prior to treatment with Tasigna
• achieved a molecular response of MR4.5 (corresponding to ≤ BCR-ABL/ABL ≤ 0.0032% IS)
• sustained an MR4.5 for a minimum of one year immediately prior to discontinuation of therapy
• been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
• no history of accelerated phase or blast crisis
• no history of prior attempts of treatment-free remission discontinuation that resulted in relapse

Monitor BCR-ABL transcript levels and complete blood count with differential in patients who have discontinued Tasigna therapy monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter [see Warnings and Precautions (5.16)].

* 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.
2.3 Reinitiation of treatment in patients who lose molecular response after discontinuation of therapy with Tasigna.

- Newly diagnosed patients who lose MMR must reinitiate treatment within 4 weeks at the dose level prior to discontinuation of therapy (see Warnings and Precautions (5.16)). Patients who reinitiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until major molecular response is re-established and every 12 weeks thereafter.
- Patients resistant or intolerant to prior treatment that included imatinib with confirmed loss of MR4.0 (2 consecutive measures separated by at least 4 weeks showing loss of 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)). Patients who reinitiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4.0 is re-established and every 12 weeks thereafter.

2.4 Dosage Modification for QT Interval Prolongation

See Table 2 for dose adjustments for QT interval prolongation (see Clinical Pharmacology (12.2)). (See Table 2) (…)

2.7 Dosage Modification for Hepatic Impairment

If possible, consider alternative therapies. If Tasigna must be administered to patients with hepatic impairment, consider the following dose reduction: (See Table 6) (…)

2.8 Dosage Modification with Concomitant Strong CYP3A4 Inhibitors

Avoid the concomitant use of strong CYP3A4 inhibitors. Should treatment with any of these agents be required, interrupt therapy with Tasigna. If patients must be coadministered a strong CYP3A4 inhibitor, reduce dosage to 300 mg once daily in patients with newly diagnosed Ph+ CML-CP. (…)

5 WARNINGS AND PRECAUTIONS

5.12 Hemorrhage

In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Tasigna and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Tasigna 300 mg bid arm, in 1.8% patients in the Tasigna 400 mg bid arm, and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Tasigna 300 mg bid and 400 mg bid arms and in 1.4% of patients in the imatinib arm, 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.

5.17 Fluid Retention

In the randomized trial in patients with newly diagnosed Ph+ CML in chronic phase, severe (Grade 3 or 4) fluid retention occurred in 3.9% and 2.9% of patients receiving Tasigna 300 mg bid and 400 mg bid, respectively, and in 2.2% of patients receiving imatinib. (…)

5.14 Effects on Growth and Development in Pediatric Patients

Growth retardation has been reported in pediatric patients with Ph+ CML in chronic phase treated with Tasigna. In a pediatric trial with 58 patients with Ph+ CML in chronic phase after a median follow-up of 33 months, 12% (n = 7) of patients experienced a decrease of two or more height percentile lines (percentile lines: 5th, 10th, 25th, 50th, 75th, 90th, and 95th). Adverse reactions associated with growth retardation were reported in 3 patients (5%). Monitor growth and development in pediatric patients receiving Tasigna treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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 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 Tasigna use in patients 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%),
### 8 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 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 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 included 18 children (age 2 to less than 12 years) and 26 adolescents (age 12 to less than 18 years).

#### 8.5 Geriatric Use

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.

#### 12 CLINICAL PHARMACOLOGY

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once or twice daily dosing. In adult patients with resistant or intolerant Ph+ CML given Tasigna 400 mg twice daily, the steady-state mean (%CV) Cmax and AUC0-12h were 1540 ng/ml (48%) and 13337 ng·h/ml (46%), respectively. In adult patients with newly diagnosed Ph+ CML given Tasigna 300 mg twice daily, the steady-state mean (%CV) Cmax and AUC0-12h were 1540 ng/ml (48%) and 13337 ng·h/ml (46%), respectively.

Specific Populations

- Age, sex, race/ethnicity, or body weight did not significantly affect the pharmacokinetics of nilotinib. The effect of renal impairment on nilotinib pharmacokinetics is unknown.

#### Pediatric Patients

Following administration of the approved 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 Ph+ CML and studies).

Body surface area correlated with nilotinib clearance and was the primary factor responsible for the PK differences between pediatrics and adults.

#### 14 CLINICAL STUDIES

**14.1 Adult Newly Diagnosed Ph+ CML-CP**

The ENEStnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Newly Diagnosed patients) study (NCT00471497) was an open-label, multicenter, randomized trial conducted to determine the efficacy of Tasigna versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were included in the study if they were aged 18 years or over and had a WHO performance status of 0 or 1.

Following assignment to treatment, patients were randomized to receive either Tasigna 400 mg twice daily or imatinib 400 mg once daily. Following randomization and at each administration, patients had a 14-day on-treatment period and then a 3-day off-treatment period. A molecular response assessment was performed every 3 months.

The ENEStnd study found that patients who received Tasigna had a significantly greater response rate than those who received imatinib. The most common adverse reactions associated with treatment included headache, nausea, vomiting, and anemia.

For more information, please refer to the labeling of Tasigna. (…)
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 the pretreatment baseline. Efficacy endpoints are summarized in Table 12. (See Table 12) (…)

14.2 Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP

Study CAMN107A2101 (referred to as Study A2101) (NCT010097107) was a single-arm, open-label, multicenter study conducted to evaluate the efficacy and safety of Tasigna (400 mg twice daily) in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic and accelerated phase disease. The definition of imatinib resistance included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance was defined as discontinuation 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-COP and 137 patients with CML-AP with a minimum follow-up of 24 months were enrolled. In this study, about 50% of CML-CP and CML-AP patients were males, over 90% (CML-CP) and 80% (CML-AP) were Caucasian, and approximately 30% were age 65 years or older.

14.3 Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)

The ENESTfreenom (Evaluating Nilotinib Efficacy and Safety in clinical Trials-freedom) study (NCT01784068) is an open-label, multicenter, single-arm study, where 215 adult patients with Ph+ CML-CP treated with Tasigna in first line for ≥ 2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 150 patients (88.4%) entered the “Treatment-free Remission” (TFR) phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

• The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year
• The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS)
• No more than two assessments falling between MR4 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤ 0.01% IS).

The median age of patients who entered the TFR phase was 55 years, 49.5% were females, and 21.1% of the patients were ≥ 65 years of age. BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:

• Loss of MMR requiring patient to reinstitute Tasigna treatment
• When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
• When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

14.4 Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5) on Tasigna following prior imatinib therapy

The ENESTtop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Stop) study (NCT01686905) is an open-label, multicenter, single-arm study, where 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥ 3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to Tasigna, then switched to Tasigna for at least 2 years), and who achieved MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

• The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during 1 year
• Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL > 0.01% IS were considered having a confirmed loss of MR4.0, triggering reinitiation of Tasigna treatment

The median time on treatment with Tasigna was 13.80 months (range: 0.7 to 30.9 months).

14.5 Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP

The safety and efficacy of Tasigna in pediatric patients with Ph+ CML-CP have been investigated in two studies: Study CAMN107A2120 (NCT01077544), an open-label, single-arm, multi-center study that evaluated the pharmacokinetics, safety, and preliminary efficacy of Tasigna in pediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib (n=11), and Study CAMN107A2203 (NCT01844765), an open-label, single-arm, multi-center study evaluating the efficacy and safety of Tasigna in Pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib (n=33) and newly diagnosed Ph+ CML-CP (n=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 400 mg). Data was pooled from a total of 69 pediatric patients (from 2 to less than 18 years of age) with either newly diagnosed Ph+ CML-CP (n=25; 6 children from 2 to less than 12 years and 19 adolescents from 12 to less than 18 years) or imatinib or dasatinib resistant or intolerant Ph+ CML-COP (n=44; 18 children from 2 to less than 12 years and 26 adolescents from 12 to less than 18 years).

The median age of patients who entered the TFR phase was 55 years, 49.5% were females, and 21.1% of the patients were ≥ 65 years of age. BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:

• When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

The median time on treatment with Tasigna was 13.80 months (range: 0.7 to 30.9 months).

14.6 Treatment discontinuation in newly diagnosed CML patients who have achieved a sustained molecular response (MR4.5)

The ENESTtop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Stop) study (NCT01686905) is an open-label, multicenter, single-arm study, where 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥ 3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to Tasigna, then switched to Tasigna for at least 2 years), and who achieved MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

• The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during 1 year
• Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL > 0.01% IS were considered having a confirmed loss of MR4.0, triggering reinitiation of Tasigna treatment

The median time on treatment with Tasigna was 13.80 months (range: 0.7 to 30.9 months).
Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2021

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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection for Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies</td>
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<td>Select patients for treatment of advanced ovarian cancer after three or more chemotherapy regimens associated with HRD positive status based on either deleterious or suspected deleterious BRCA mutation and/or genomic instability score (GIS) [see Clinical Studies (14.3)]. Information on FDA-approved tests for the detection of either deleterious or suspected deleterious BRCA mutation or genomic instability for this indication is available at:</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer</td>
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|                                        |            |                   |            |                   | (…) Patients were randomized post completion of first-line platinum-based chemotherapy plus surgery. Randomization was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (yes vs no), and HRD status (positive vs negative or not determined). HRD status was determined using the FDA-approved Myriad myChoice CDx assay. HRD positive status included either tumor BRCA mutant (tBRCAm) or a genomic instability score (GIS) ≥ 42. (…)
|                                        |            |                   |            |                   | 14.2 Maintenance Treatment of Recurrent Ovarian Cancer |
|                                        |            |                   |            |                   | Randomization was stratified by time to progression after the penultimate platinum therapy (6 to <12 months and ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no); and best response during the most recent platinum regimen (complete response and partial response). Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline BRCA mutations (gBRCAm) were assigned to the germline BRCA mutated (gBRCAmut) cohort (n=203), and those without germline BRCA mutations were assigned to the non-gBRCAmut cohort (n=350). (…)
|                                        |            |                   |            |                   | 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). |
|                                        |            |                   |            |                   | 14.3 Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies |
|                                        |            |                   |            |                   | The efficacy of ZEJULA was studied in 98 patients with advanced ovarian cancer with HRD positive tumors in the single-arm QUADRA (NCT02545856) trial. Patients were required to have been treated with three or more prior lines of chemotherapy and those with prior exposure to PARP inhibitors were excluded. Patients were selected using a clinical trial assay. Those without BRCA mutations must have progressed at least six months after their last dose of platinum therapy. All patients received ZEJULA capsules at a starting dose of 300 mg once daily as monotherapy until disease progression or unacceptable toxicity. HRD positive status was determined using the Myriad myChoice CDx as either tBRCAm (n=63) and/or a genomic instability score (GIS) ≥ 42 (n=35). GIS is an algorithmic measurement of Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI), and Large-scale State Transitions (LST). (See Table 14) (…) |
|                                        |            |                   |            |                   | For patients with tBRCAm ovarian cancer, investigator-assessed ORR was 39% (7/18; 95% CI: [17, 64]) in patients with platinum-sensitive disease, 29% (6/21; 95% CI: [11, 52]) in patients with platinum-resistant disease, and 19% (3/16; 95% CI: [4, 46]) in patients with platinum-refractory disease. |
|                                        |            |                   |            |                   | Patients were randomized post completion of first-line platinum-based chemotherapy plus surgery. Randomization was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (yes vs no), and HRD status (positive vs negative or not determined). HRD status was determined using the FDA-approved Myriad myChoice CDx assay. HRD positive status included either tumor BRCA mutant (tBRCAm) or a genomic instability score (GIS) ≥ 42. (…)
|                                        |            |                   |            |                   | 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). |
|                                        |            |                   |            |                   | 14.4 Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies |
|                                        |            |                   |            |                   | The efficacy of ZEJULA was studied in 98 patients with advanced ovarian cancer with HRD positive tumors in the single-arm QUADRA (NCT02545856) trial. Patients were required to have been treated with three or more prior lines of chemotherapy and those with prior exposure to PARP inhibitors were excluded. Patients were selected using a clinical trial assay. Those without BRCA mutations must have progressed at least six months after their last dose of platinum therapy. All patients received ZEJULA capsules at a starting dose of 300 mg once daily as monotherapy until disease progression or unacceptable toxicity. HRD positive status was determined using the Myriad myChoice CDx as either tBRCAm (n=63) and/or a genomic instability score (GIS) ≥ 42 (n=35). GIS is an algorithmic measurement of Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI), and Large-scale State Transitions (LST). (See Table 14) (…) |
|                                        |            |                   |            |                   | For patients with tBRCAm ovarian cancer, investigator-assessed ORR was 39% (7/18; 95% CI: [17, 64]) in patients with platinum-sensitive disease, 29% (6/21; 95% CI: [11, 52]) in patients with platinum-resistant disease, and 19% (3/16; 95% CI: [4, 46]) in patients with platinum-refractory disease. |
| 009175, 11/04/2013                     | Nitrofurantoin | Infectious Diseases | G6PD | Warnings, Adverse Reactions | WARNINGS |
|                                        |            |                   |            |                   | Hemolytic anemia |
|                                        |            |                   |            |                   | Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolyisis appears to be linked to a glucose-6-phosphatedehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolyisis is an indication for discontinuing Furadantin; hemolyisis ceases when the drug is withdrawn. |
|                                        |            |                   |            |                   | ADVERSE REACTIONS |
|                                        |            |                   |            |                   | Laboratory Adverse Events |
|                                        |            |                   |            |                   | The following laboratory adverse events have been reported with the use of nitrofurantoin; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see Warnings), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely. |

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| 125554, 07/23/2021                     | Nivolumab (1) | Oncology | BRAF | Adverse Reactions, Clinical Studies | 6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Unresectable or Metastatic Melanoma  
Previously Treated Metastatic Melanoma  
(…) In CHECKMATE-037, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (…)  
Previously Untreated Metastatic Melanoma  
CHECKMATE-066  
The safety of OPDIVO was also evaluated in Trial 4, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m² every 3 weeks (n=205) [see Clinical Studies (14.1)]. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. (…)  
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%), elevated LDH (56%), history of brain metastases (16%), 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. <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 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%), 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%). (…) |
| 125554, 07/23/2021                     | Nivolumab (2) | Oncology | CD274 (PD-L1) | Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
1.3 Metastatic Non-Small Cell Lung Cancer  
• OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations.  
2 DOSAGE 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 570 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 396 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)]. (…)  
12.3 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, solid tumor type, tumor size, renal impairment (eGFR ≥ 15 mL/min/1.73 m²), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST). |

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14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

CHECKMATE-066

Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). (…)

Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma 44 Reference ID: 4198384 (11%), elevated LDH level (37%), PD-L1 greater than or equal to 5% tumor cell membrane expression (33%), and history of brain metastasis (4%). (…)

CHECKMATE-067

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay. BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). (…)

The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (88%); 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

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 IIIIC vs Stage IV vs Stage IV M1c). (…)

Disease characteristics were AJCC Stage IIIb (34%), Stage IIIC (47%), 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)

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [IASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. (…)

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous vs squamous). (…)

In Part 1a, a total of 793 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers.

The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the OPDIVO and ipilimumab arm compared with the platinum-doublet chemotherapy arm. The OS results are presented in Table 35 and Figure 5. (…)

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

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC], ECOG performance status 0 or 1, and no prior anticancer therapy [including EGFR and ALK inhibitors] for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. 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 maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression status (≥1% or <1% or nonquantifiable), histology (squamous versus non-squamous), and sex (male versus female). (…)

A total of 719 patients were randomized to receive either OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 87) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (88%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 52% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers. (…)

Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-457

This study included patients regardless of their PD-L1 status. (…)

Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the study population, 17% (47/272) of patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% (106/225) had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1, and 53% (119/225) had PD-L1 positive squamous NSCLC, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.98 (95% CI: 0.37, 2.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.40, 1.05) in the PD-L1 positive NSCLC subgroup. (…)

Second-line Treatment of Metastatic Non-Squamous NSCLC

CHECKMATE-057

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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.

14.8 Urothelial Carcinoma

CHECKMATE-275

(…) Patients were included regardless of their PD-L1 status. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 27. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%). (see Table 45)

14.11 Esophageal Squamous Cell Cancer

ATTRACTION-3 (NCT02569942) was a multicenter, randomized (1:1), active-controlled, open-label trial in patients with unresectable advanced, recurrent, or metastatic ESCC, who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen. The trial enrolled patients regardless of PD-L1 status, but tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. (…) Randomization was stratified by region (Japan vs. Rest of World), number of organs with metastases (≥1 vs. ≥2), and PD-L1 status (≥1% vs. <1% or indeterminate). (…) ATTRACTION-3 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice of taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. The minimum follow-up was 17.6 months. Efficacy results are shown in Table 48 and Figure 14.

Of the 419 patients, 48% had PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. The remaining 52% had PD-L1 negative ESCC defined as <1% of tumor cells expressing PD-L1. In a pre-specified exploratory analysis by PD-L1 status, the hazard ratio (HR) for OS was 0.59 (95% CI: 0.44, 0.81) with median survivals of 10.9 and 8.1 months for the OPDIVO and investigator's choice arms, respectively. In the PD-L1 negative subgroup, the HR for OS was 0.84 (95% CI: 0.47, 1.47) with median survivals of 10.9 and 9.3 months for the OPDIVO and investigator's choice arms, respectively.

14.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

CHECKMATE-649 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. (…) Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (mFOLFOX6 vs. CapeOX). The major efficacy outcome measures, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Additional efficacy outcome measures included OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and ORR and DOR assessed by BICR in patients with PD-L1 CPS ≥1 and ≥5, and in all randomized patients. Tumor assessments were conducted per RECIST v1.1 every 6 weeks up to and including week 48, then every 12 weeks thereafter. (…) CHECKMATE-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 60 and Figures 19, 20, and 21.

In an exploratory analysis in patients with PD-L1 CPS=1 (n=265), the median OS was 13.1 months (95% CI: 9.8, 16.7) for the OPDIVO and chemotherapy arm and 12.5 months (95% CI: 10.1, 13.8) for the chemotherapy arm, with a stratified HR of 0.85 (95% CI: 0.63, 1.15). In an exploratory analysis in patients with PD-L1 CPS<5 (n=606), the median OS was 12.4 months (95% CI: 10.6, 14.3) for the OPDIVO and chemotherapy arm and 12.3 months (95% CI: 11.0, 13.2) for the chemotherapy arm, with a stratified HR of 0.84 (95% CI: 0.76, 1.14). (…)

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<td>The safety and effectiveness of OPDIVO have been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence of adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater for this indication is the same as that in adults (see Dosage and Administration (2.8), Clinical Pharmacology (12.3), and Clinical Studies (14.1)). The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients less than 18 years old for the other approved indications.</td>
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</tbody>
</table>
| 07/23/2021 | Nivolumab (4) | Oncology | EGFR | Indications and Usage, Adverse Reactions, Clinical Studies | **14 CLINICAL STUDIES**

**14.9 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer**

CHECKMATE-142 (NCT02690188) was a multicenter, open-label, single-arm study conducted in patients with locally determined dMMR or MSI-H metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. (…) Patients enrolled in the single-agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) once every 2 weeks. Patients enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg IV every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg IV as a single agent every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (…) A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥75 years of age, 55% were male, and 88% were White. (…) A total of 119 patients were enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort. (See Table 56) (…) |

| 125554, 07/23/2021 | | | | | **14 CLINICAL STUDIES**

**14.10 Metastatic Non-Small Cell Lung Cancer**

First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations (see Clinical Studies (14.3)). (…) |

| | | | | | **14 CLINICAL STUDIES**

**14.13 Metastatic Non-Small Cell Lung Cancer**

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

The safety and effectiveness of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. (…) The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥75 years of age, 59% were male and 88% were White. (…) A total of 119 patients were enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort. (See Table 56) (…) |

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<th>Labeling Sections</th>
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| 125544, 07/23/2021                     | Nivolumab (5) | Oncology | ALK | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.3 Metastatic Non-Small Cell Lung Cancer
• OPDIVO, 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.
• OPDIVO, 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 non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
• OPDIVO is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. |

6 ADVERSE REACTIONS
Metastatic Non-Small Cell Lung Cancer
First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab
The safety of OPDIVO 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 (14.3)] (…).

14 CLINICAL STUDIES
14.3 Metastatic Non-Small Cell Lung Cancer
First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab
CHECKMATE-227 (NCT02471926) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. (…)

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doubled Chemotherapy
CHECKMATE-569 (NCT02357076) 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. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment. (…)

Second-line Treatment of Metastatic Non-Squamous NSCLC
(…) CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior Platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. (…)

The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (62%) and male (50%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. (…)

| 125544, 07/23/2021 | Nivolumab (8) | Oncology | EHR2 (HER2) | Adverse Reactions, Clinical Studies | 6 ADVERSE REACTIONS
Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
The safety of OPDIVO in combination with chemotherapy was evaluated in CHECKMATE649, a randomized, multicenter, open-label trial in patients who previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma [see Clinical Studies (14.12)].
The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

14 CLINICAL STUDIES
14.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma CHECKMATE-069 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases.

| 018013, 04/09/2019 | Nortriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS
Drugs Metabolized by P450 2D6
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 10%). Those patients are 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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<td>209531, 10/10/2018</td>
<td>Nusinersen</td>
<td>Neurology</td>
<td>SMN2</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY: 12.2 Pharmacodynamics: Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants.</td>
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<td>125488, 03/27/2020</td>
<td>Obinutuzumab</td>
<td>Oncology</td>
<td>MS4A1 (CD20 antigen)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES: 14.1 Infantile-Onset SMA: ... 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. ... 14.3 Presymptomatic SMA: ... 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>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td>14 CLINICAL STUDIES: 14.1 Chronic Lymphocytic Leukemia: GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (Study 1) in 781 patients with previously untreated CD20+ chronic lymphocytic leukemia requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) &lt; 70 mL/min. (…)</td>
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| 12/07/2020   | 208558, 12/07/2020                    | Olaparib (2) | Oncology          | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874553), 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 with unacceptable toxicity or progressive disease. (…)
All patients had a deleterious or suspected deleterious germline BRCA mutation and were treated with three or more prior lines of chemotherapy. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant, or metastatic setting. (…)
Of the 362 patients randomized to SOLO-2, 299 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. (…)
| Study 19     |                                      |            |                   |            |                   | A retrospective analysis for germline BRCA mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious gBRCA mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo. (…)
14.4 Advanced Germline BRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy
The efficacy of Lynparza was investigated in a single-arm study of patients with deleterious or suspected deleterious gBRCAm advanced cancers. A total of 137 patients with measurable, advanced gBRCAm ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules 400 mg orally twice daily until disease progression or intolerable toxicity. The efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by the investigator according to RECIST, version 1.0. (…)
14.5 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 concomitantly) and a taxane, in the neoadjuvant, adjuvant, or metastatic setting. (…)
Of the 302 patients randomized onto OlympiAD, 299 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 (NCT02184195), 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, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized in Cohort B; patients with comutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A. (…)
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 pFSF 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><strong>208558, 12/07/2020</strong></td>
<td>Olaparib (3)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<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 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 orchietomy.</td>
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<td><strong>208558, 12/07/2020</strong></td>
<td>Olaparib (4)</td>
<td>Oncology</td>
<td>BRCA, Genomic Instability (Homologous Recombination Deficiency)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>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)].</td>
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| 208558, 12/07/2020 | Olaparib (5) | Oncology | Homologous Recombination Repair | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 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

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years who, in the opinion of the treating healthcare 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 platinum-based chemotherapy and outcome of cytoreductive surgery and response to platinum-based chemotherapy and IBRCAm 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) (…)

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- First-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma.
- HRG gene-mutated metastatic castration-resistant prostate cancer Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchectomy.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trial Experience

HRG Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound:
The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRG gene mutations who had progressed following prior treatment with enzalutamide or abiraterone in PROfound [see Clinical Studies (14.7)].

#### 14 CLINICAL STUDIES

**14.7 HRG Gene-mutated Metastatic Castration-Resistant Prostate Cancer**

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), randomized, open-label, multicenter trial that evaluated the efficacy of Lynparza 300 mg twice daily versus a comparator arm of investigator’s choice of enzalutamide or abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC). All patients received a GnRH analog or had prior bilateral orchectomy. Patients needed to have progressed on prior enzalutamide or abiraterone for the treatment of metastatic prostate cancer and/or CRPC and have a tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.

Patients were divided into two cohorts based on HRG gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized in Cohort B; patients with comutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A. Although patients with PPP2R2A gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit. (…)

Patients with HRG gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRG assay performed at a central laboratory. Determination of deleterious or suspected deleterious somatic or germline HRG 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 HRG genes: FANCL and RAD51C. (See Table 25) (…)

Response data by HRG mutations for patients in the Lynparza arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an ATM mutation alone and 2 patients with co-occurring mutations (one with PALB2+PPP2R2A and one with CDK12+PALB2). (See Table 27) (…)

#### 14.7.7 HRG Gene-mutated Metastatic Castration-Resistant Prostate Cancer

(…) Patients were divided into two cohorts based on HRG gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized in Cohort B; patients with comutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A. Although patients with PPP2R2A gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit. (See Tables 25 and 26) (…)

Response data by HRG mutations for patients in the Lynparza arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an ATM mutation alone and 2 patients with co-occurring mutations (one with PALB2+PPP2R2A and one with CDK12+PALB2). (See Table 27) (…)

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† 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 of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2021**

<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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<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>7 DRUG INTERACTIONS</strong></td>
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<tr>
<td>(…) Patients who are CYP2D6 normal metabolizers taking a CYP2D6 inhibitor, and a strong CYP3A4 inhibitor (or discontinuation of CYP3A4 inducers) may require less frequent dosing. Patients who are known CYP2D6 poor metabolizers and taking a CYP3A4 inhibitor (or discontinuation of CYP3A4 inducers) may 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. (…)</td>
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</tbody>
</table>

**8 USE IN SPECIFIC POPULATIONS**

### 8.8 Poor Metabolizers of CYP2D6 Substrates

In patients who are known or suspected to be poor CYP2D6 metabolizers, based on genotype or previous history/experience with other CYP2D6 substrates, less frequent dosing of OLINVYK may be required. These patients should be closely monitored, and subsequent doses should be based on the patient’s severity of pain and response to treatment. [See Warnings and Precautions (5.6), Clinical Pharmacology (12.5)].

**12 CLINICAL PHARMACOLOGY**

### 12.3 Pharmacokinetics

**Drug Interaction Studies**

In vitro studies suggest that oliceridine is metabolized primarily by the CYP3A4 and CYP2D6 P450 hepatic enzymes, with minor contributions from CYP2C9 and CYP2C19. Inhibition studies using selective inhibitors of all the major CYP enzymes show that only the inhibition of CYP3A4 and CYP2D6 significantly affects the metabolism of oliceridine in these assays, suggesting that the contribution of CYP2C9 and CYP2C19 to the metabolism of oliceridine is minor. The effect of concomitant administration of a CYP2D6 inhibitor on the pharmacokinetics of OLINVYK, although not studied, may be similar to that noted in subjects who are CYP2D6 poor metabolizers. The plasma clearance of oliceridine in CYP2D6 poor metabolizers is approximately 50% of plasma clearance in subjects who are nonpoor CYP2D6 metabolizers [See Pharmacogenomics (12.5)].

In healthy subjects CYP2D6 poor metabolizers (n=4) given a single 0.25 mg dose of OLINVYK after 5 days of itraconazole 200 mg QD (a strong CYP3A4 inhibitor), the total exposure (AUC) of OLINVYK was increased by approximately 80%; however, the peak concentration was not significantly affected [See Pharmacogenomics 12.5]. The mean clearance of oliceridine was reduced to approximately 30% of that observed in nonpoor metabolizers of CYP2D6 [see Drug Interactions (7)].

### 12.5 Pharmacogenomics

Oliceridine is metabolized by polymorphic enzyme CYP2D6. CYP2D6 poor metabolizers have little to no enzyme activity. Approximately 3 to 10% of Whites, 2 to 7% of African Americans, and <2% of Asians, generally lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. In healthy subjects who are CYP2D6 poor metabolizers, the AUC0-inf of oliceridine was approximately 2-fold higher than in subjects who are nonpoor CYP2D6 metabolizers. [see Warnings and Precautions (5.6), Use in Specific Populations (8.8)].
# Table of Pharmacogenomic Biomarkers in Drug Labeling

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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>020007, 03/08/2017</td>
<td>Ondansetron</td>
<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td></td>
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<td>12.3 Pharmacokinetics</td>
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<td>Metabolism</td>
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<td>(…) The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolisers of CYP2D6 and those who were extensive metabolisers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo. (…)</td>
</tr>
<tr>
<td>208065, 12/18/2020</td>
<td>Osimertinib</td>
<td>Oncology</td>
<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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<td></td>
<td>1.1 Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>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)].</td>
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<td>1.2 First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC</td>
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<td>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)].</td>
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<td>1.3 Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC</td>
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<td>TAGRISSO is indicated for the treatment of adult patients with metastatic EGF T790M mutationpositive 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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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection</td>
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<td>Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens [see Clinical Studies (14)].</td>
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<td>Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens [see Clinical Studies (14)]. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.</td>
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<td>Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TAGRISSO following progression on or after EGFR TKI therapy based on the presence of an EGF T790M mutation in tumor or plasma specimens [see Clinical Studies (14)]. Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.</td>
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<td>Information on FDA-approved tests for the detection of EGFR mutations is available at <a href="http://www.fda.gov/companiondiagnostics">http://www.fda.gov/companiondiagnostics</a>.</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>(…) The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials [ADURA (n=337), FLAURA (n=279), and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) [see Warnings and Precautions (5)]. The data described below reflect exposure to TAGRISSO (80 mg daily) in 337 patients with EGFR mutation-positive resectable NSCLC, and 558 patients with EGFR mutation-positive metastatic NSCLC in three randomized, controlled trials [ADURA (n=337), FLAURA (n=279), and AURA3 (n=279)]. With a history of interstitial lung disease, drug induced interstitial disease or radiationpneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies. (…)</td>
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<td>Adjuvant Treatment of EGFR Mutation-Positive NSCLC</td>
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<td>The safety of TAGRISSO was evaluated in ADURA1, a randomized, double-blind, placebo-controlled trial for the adjuvant treatment of patients with EGF exon 19 deletions or exon 21 L858R mutationpositive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 22.5 months. (…)</td>
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<td>Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer</td>
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<td>The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutationpositive, or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. (See Tables 4 and 5) (…)</td>
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<td></td>
<td>Previously Treated EGFR T790M Mutation-Positive Metastatic Non-Small Cell Lung Cancer</td>
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<td>The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGF T790M mutationpositive NSCLC who had progressive disease following first line EGFR TKI therapy. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<tr>
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<td></td>
<td>14.1 Adjuvant Treatment of Early-Stage EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>The efficacy of TAGRISSO was demonstrated in a randomized, double-blind, placebo-controlled trial [ADURA (NCT02511106)] for the adjuvant treatment of patients with EGFR exon 19 deletions or exon 21 L858R mutationpositive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. Eligible patients with resectable tumors (stage IB – IIa) according to American Joint Commission on Cancer (AJCC) 7th edition were required to have predominantly non-squamous histology and EGFR exon 19 deletions or exon 21 L858R mutations identified prospectively from tumor tissue in a central laboratory by the cobas® EGFR Mutation Test. Patients with clinically significant uncontrolled cardiac disease, prior history of ILD/pneumonitis, or who received treatment with any EGFR kinase inhibitor were not eligible for the study.</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.
Patients were randomized (1:1) to receive TAGRISSO 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy if given. Patients who did not receive adjuvant chemotherapy were randomized within 10 weeks and patients who received adjuvant chemotherapy were randomized within 26 weeks following surgery. Randomization was stratified by mutation type (exon 19 deletions or exon 21 L858R mutations), race (Asian or non-Asian) and pTNM staging (IB or IIIA or IIIA) according to AJCC 7th edition. Treatment was given for 3 years or until disease recurrence, or unacceptable toxicity. The major efficacy outcome measure was disease-free survival (DFS, defined as reduction in the risk of disease recurrence or death) in patients with stage II – IIIA NSCLC determined by investigator assessment. Additional efficacy outcome measures included DFS in the overall population (patients with stage IB – IIIA NSCLC) and overall survival (OS) in patients with stage II – IIIA NSCLC and in the overall population. A total of 682 patients were randomized to TAGRISSO (n=339) or placebo (n=343). The median age was 63 years (range 30-86 years); 70% were female; 64% were Asian and 72% were never smokers. Baseline WHO performance status was 0 (64%) or 1 (36%); 31% had stage IB, 35% II, and 34% IIIA. With regard to EGFR mutation status, 55% were exon 19 deletions and 45% were exon 21 L858R mutations. The majority (60%) of patients received adjuvant chemotherapy prior to randomization (27% IB; 70% II, 79% IIIA). (See Table 8) (…)

### 13.2 Previously Untreated EGFR Mutation-Positive Metastatic NSCLC

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter, double-blind, active-controlled trial (FLAURA [NCT02296125]) in patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, metastatic NSCLC, who had not received previous systemic treatment for metastatic disease. Patients were required to have measurable disease per RECIST v1.1, a WHO performance status of 0-1, and EGFR exon 19 deletions or exon 21 L858R mutation in tumor prospectively identified by the cobas® EGFR Mutation Test in a central laboratory or by an investigational assay at a CLIA-certified or accredited laboratory. Patients with CNS metastases not requiring steroids and with stable neurologic status for at least two weeks after completion of definitive surgery or radiotherapy were eligible. Patients were assessed at the investigator’s discretion for CNS metastases if they had a history of, or suspected, CNS metastases at study entry. Patients were randomized (1:1) to receive TAGRISSO 80 mg orally once daily or to receive gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by EGFR mutation type (exon 19 deletions or exon 21 L858R mutation) and ethnicity (Asian or non-Asian). Patients randomized to the control arm were offered TAGRISSO at the time of disease progression if tumor samples tested positive for the EGFR T790M mutation. The major efficacy outcome measure was progression-free survival (PFS), as assessed by investigator. Additional efficacy outcome measures included overall survival (OS) and overall response rate (ORR). A total of 556 patients were randomized to TAGRISSO (n=279) or to control (gefitinib n=183; erlotinib n=194). The median age was 64 years (range 26-93 years); 54% were <65 years of age; 63% were female; 62% were Asian and 64% were never smokers. Baseline WHO performance status was 0 (41%) or 1 (59%); 5% had Stage IIb and 95% had Stage IV; and 7% received prior systemic cytotoxic chemotherapy as neoadjuvant or adjuvant therapy. With regard to tumor testing, 63% were exon 19 deletions and 37% were exon 21 L858R; 5 patients (<1%) also had a concomitant de novo T790M mutation. EGFR mutation status was confirmed centrally using the cobas EGFR Mutation Test in 90% of patients. At the time of the final data cut-off, of those randomized to TAGRISSO and to investigator’s choice erlotinib or gefitinib arm, 133 (48%) and 180 (65%) patients had received at least one subsequent treatment, respectively. Out of the 180 patients randomized to erlotinib or gefitinib who received subsequent treatment, 85 (47%) patients received TAGRISSO as first subsequent therapy. (See Table 9) (…)

### 14.2 Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter open-label, active-controlled trial in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI (AURA3). All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas® EGFR Mutation Test performed in a central laboratory prior to randomization. (…)
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<table>
<thead>
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<th>Biomarker†‡</th>
<th>Labeling Sections</th>
<th>Labeling Text†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>208032, 11/02/2018</td>
<td>Oxymetazoline and Tetracaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>Human Leukocyte Antigen (HLA) allele B<em>1502 increases the risk for developing SJS/TEN in patients treated with carbamazepine. The chemical structures of immediate release oxicarbazepine and Oxtellar XR are similar to that of carbamazepine. Available clinical evidence, and data from nonclinical studies showing a direct interaction between immediate release oxicarbazepine and HLA-B</em>1502 protein, suggest that the HLA-B<em>1502 allele may also increase the risk for SJS/TEN with Oxtellar XR. The frequency of HLA-B</em>1502 allele ranges from 2 to 12% in Han Chinese populations, is about 8% in Thai populations, and above 15% in the Philippines and in some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B<em>1502 allele is negligible in people from European descent, several African populations, some indigenous peoples of the Americas, and in Japanese (&lt;1%). Testing for the presence of the HLA-B</em>1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Oxtellar XR. The use of Oxtellar XR should be avoided in patients positive for HLA-B<em>1502 unless the benefits clearly outweigh the risks. Consideration should also be given to avoid the use of other drugs associated with SJS/TEN in HLA-B</em>1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B<em>1502 is low, or in current Oxtellar XR users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B</em>1502 status. 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 well characterized.</td>
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<tr>
<td>208032, 11/02/2018</td>
<td>Oxymetazoline and Tetracaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions</td>
<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>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 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>207103, 09/09/2019</td>
<td>Palbociclib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<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>
</tr>
</tbody>
</table>

| 021999, 01/25/2019 | Paliperidone | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination (…) Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. (…) |

| 021372, 09/18/2014 | Palonosetron | Gastroenterology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-Hydroxy-palonosetron. These metabolites each have less than 1% of the 5- HT3 receptor 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, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates. |

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Table of Pharmacogenomic Biomarkers in Drug Labeling

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| 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 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 20050203 are limited to 656 patients with wild-type KRAS mCRC. The safety profile of Vectibix in patients with wild-type RAS mCRC is similar with that seen in patients with wild-type KRAS mCRC.  

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 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 RAS mCRC. (...)

| 125147, 06/29/2017                     | Panitumumab (2) | Oncology | RAS | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 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 inotocan-containing chemotherapy [see Clinical Studies (14.1)].  
Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown [see Dosage and Administration (2.1), Warnings and Precautions (5.2), and Clinical Pharmacology (12.1)].  

2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Prior to initiation of treatment with Vectibix, assess RAS mutational status in colorectal tumors and confirm the absence of a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of both KRAS and NRAS. Information on FDA-approved tests for the detection of RAS mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/CompanionDiagnostics.  

5 WARNINGS AND PRECAUTIONS  
5.2 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with RAS-Mutant mCRC  
Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereafter is referred to as “RAS” [see Indications and Usage (1.1), Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)].  
Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of RAS mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing RAS mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents [see Indications and Usage (1.1), and Clinical Pharmacology (12.1)].  
Additionally, in Study 20050203, 272 patients with RAS-mutant mCRC tumors received Vectibix in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with RAS-mutant mCRC who received Vectibix and FOLFOX versus FOLFOX alone [see Indications and Usage (1.1)].  

6 ADVERSE REACTIONS  
The following adverse reactions are discussed in greater detail in other sections of the label:  
• (…) Increased Tumor Progression, Increased Mortality, or Lack of Benefit in RAS-Mutant mCRC [see Indications and Usage (1.1) and Warnings and Precautions (5.2)] (…)  
6.1 Clinical Trials Experience  
(...)
Safety data are presented from two clinical trials in which patients received Vectibix: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 20050203 are limited to 656 patients with wild-type KRAS mCRC. The safety profile of Vectibix in patients with wild-type RAS mCRC is similar with that seen in patients with wild-type KRAS mCRC. (...)

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<td><strong>Vectibix in Combination with FOLFOX Chemotherapy</strong></td>
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<td><strong>14 CLINICAL STUDIES</strong></td>
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<td><strong>14.1 Recurrent or Refractory mCRC</strong></td>
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<td>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. Study 20080763 (NCT008763was an open label, multicenter, multinational, randomized (1:1) clinical trial, stratified by region (North America, Western Europe, and Australia versus rest of the world) and ECOG PS (0 and 1 vs 2) in patients with wild-type KRAS mCRC. (See Table 3 and Figure 1) (…) Study 20100007 (NCT01412957) 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 major efficacy outcome measure was OS in patients with wild-type KRAS mCRC. Secondary efficacy outcome measures included OS in the subgroup of patients with wild-type RAS mCRC; PFS and ORR in patients with wild-type KRAS; and PFS and ORR in the subgroup of patients with wild-type RAS mCRC. (…) KRAS tumor mutation status was available for all patients and RAS tumor mutation status was available for 86% of the 377 patients. Among the 377 patients, 270 (72%) patients had wild-type RAS tumors, 54 (14%) had mutant RAS tumors, and 54 (14%) had unknown RAS tumor status. (See Table 4 and Figure 2)</td>
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<td><strong>14.2 First-line in Combination with FOLFOX Chemotherapy</strong></td>
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<td>(…) 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 = 664), 66% 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) (…) 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 with wild-type KRAS mCRC 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) Retroactive 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 1, 2, 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)</td>
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<td><strong>14.3 RAS-Mutant mCRC</strong></td>
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<td>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 mCRC, 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</td>
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</table>
| 020987, 04/25/2019 | Pantoprazole | Gastroenterology | CYP2C19 | Clinical Pharmacology | Patients with Hepatic Impairment
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.

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<th>125511, 12/17/2018</th>
<th>Parathyroid Hormone</th>
<th>Inborn Errors of Metabolism</th>
<th>CASR</th>
<th>Indications and Usage, Clinical Studies</th>
</tr>
</thead>
</table>
| 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.

14 CLINICAL STUDIES
Study in Patients with Established Hypoparathyroidism
(…)

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<th>Psychiatry</th>
<th>CYP2D6</th>
<th>Drug Interactions, Clinical Pharmacology</th>
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| 6 ADVERSE REACTIONS
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| 12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
(…)
| 14 CLINICAL STUDIES
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<th>Oncology</th>
<th>UGT1A1</th>
<th>Clinical Pharmacology</th>
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| 12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
|
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<td>Pazopanib (2)</td>
<td>Oncology</td>
<td>HLA-B</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; 3 X ULN (NCI CTC Grade 2) occurred in 32% (42/133) of HLA-B<em>57:01 allele carriers and in 19% (397/2101) of non-carriers and ALT &gt; 5 X 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 be monitored in all subjects receiving pazopanib, regardless of genotype [see Warnings and Precautions (5.1)].</td>
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<tr>
<td>103949, 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 A retrospective genome-wide association analysis1,2 of 1671 subjects (1040 subjects from Study 4 [see Clinical Studies (14.1)] and 67 subjects from another clinical trial) was performed to identify human genetic contributions to anti-HCV treatment response in previously untreated HCV genotype 1 subjects. A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (IL28B rs12979860) was associated with variable SVR rates. The rs12979860 genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1587), SVR rates by rs12979860 genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to IL28B genotype was consistent across various racial/ethnic groups (see Table 14). Other variants near the IL28B gene (e.g., rs8099917 and rs8013142) have been identified; however, they have not been shown to independently influence SVR rates during treatment with pegylated interferon alpha therapies combined with ribavirin. [See Table 13]</td>
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<td>125293, 07/13/2018</td>
<td>Pegloticase</td>
<td>Rheumatology</td>
<td>G6PD</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 (4.3).</td>
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<tr>
<td>125514, 07/21/2021</td>
<td>Pembrolizumab (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (ipilimumab-Refractory Melanoma) The safety of KEYTRUDA in patients with unseetable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. (…)</td>
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<tr>
<td>125514, 07/21/2021</td>
<td>Pembrolizumab</td>
<td>Oncology</td>
<td>CD274</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>(…) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with resectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. (…) Twenty-three percent of patients were BRAF 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. (…) Melanoma ipilimumab-Refractory Melanoma (…) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with resectable 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 unaltered 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 88 years); 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 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 IICC (1-3 positive lymph nodes), and 20% had stage IIC (≥4 positive lymph nodes); 50% were BRAF V6000 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IJO assay.</td>
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| 1.10 Esophageal Cancer                   | Keytruda, as a single agent, 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 ≥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 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. |

| 1.11 Cervical Cancer                    | Keytruda, as a single agent, 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 ≥1) 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. |

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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 (14.1)]. 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>1.18 Triple-Negative Breast Cancer</td>
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<td>KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unrespectable 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.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H Cancer, or TMB-H Cancer</td>
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<td>(…) 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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. An FDA-approved test for the detection of MSI-H or dMMR is not currently available. (See Table 2)</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>Previously Untreated NSCLC</td>
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<td>The safety and effectiveness 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)]. (…)</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 KEYTRUDA as a single agent have been established in pediatric patients with cHL, PMBC, 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 pharmacoepidemiologic 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 compared to adults included pyrexia (33%), vomiting (30%), upper respiratory tract infection (29%), and headache (25%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients 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)].</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Melanoma</td>
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<td>Ipilimumab-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. &lt;1% of tumor cells [negative]) according to an investigational use only (IUCO) 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 of 0; 80% had PD-L1 positive melanoma. 18% had PS-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUCO assay; 65% had M1c stage disease; 68% with normal LDH; 36% with reported BRAF mutation positive melanoma; and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. (…) Appropriate 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% EOCG PS of 0 and 6% EOCG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (4-6 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1 according to an IUCO assay. (…)</td>
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</tbody>
</table>

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<thead>
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<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Biomarker†</th>
<th>Labeling Sections</th>
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<td>For patients with PD-L1 positive tumors, the HR was 0.54 (95% CI: 0.42, 0.69); p&lt;0.001. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.</td>
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<td><strong>14.2 Non-Small Cell Lung Cancer</strong></td>
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<td><strong>First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy</strong></td>
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<td>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 (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS &lt;1% [negative] vs. TPS ≥1%). (…) First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy</td>
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<td>TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 37 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%. For patients with PD-L1 expression TPS &lt;1% [negative], 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).</td>
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<td><strong>KEYNOTE-042</strong></td>
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<td>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. Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and pretreatment chemotherapy (yes vs. no). The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 37 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%. (See Table 37) (…) The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% 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).</td>
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<td><strong>KEYNOTE-024</strong></td>
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<td>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 were eligible. (…) Previously treated NSCLC</td>
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<td>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 progression following platinum-containing chemotherapy, and in 332 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy and in 332 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy and had received at least 1 prior line of chemotherapy, or had insufficient progress in any line of previously received platinum doublets. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS &lt;1% [negative] vs. TPS ≥1%). (…) The trial demonstrated a statistically significant improvement in OS for patients with PD-L1 expression TPS &lt;1% [negative], 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).</td>
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<td>125514, 07/21/2021 Pembrolizumab</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>Among the 98 patients in Cohort E, 77 (79%) 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 75); 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. 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), a randomized, multicenter, open-label trial conducted in 861 patients who had not 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 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 ≥ 10. Table 58 and Figure 16 summarize the efficacy results for KEYNOTE-355.</td>
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<th>Date</th>
<th>Drug</th>
<th>Oncology</th>
<th>EGFR</th>
<th>Indications and Usage, Adverse Reactions, Clinical Studies</th>
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<td>12/21/2014</td>
<td>Pembrolizumab (4)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
<td>1.2 Non-Small Cell Lung Cancer</td>
<td>KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor alterations.</td>
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<td><strong>1.2 Non-Small Cell Lung Cancer</strong></td>
<td>Pembrolizumab (5)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td><strong>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.</strong>&lt;br&gt;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:&lt;br&gt;• stage III where patients are not candidates for surgical resection or definitive chemoradiation, or&lt;br&gt;• metastatic.&lt;br&gt;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>Oncology</td>
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<td>Tumor Mutational Burden</td>
<td>Indications and Usage, Dosage, Administration, Clinical Studies</td>
<td>KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test [see Dosage and Administration (2.1)], that have progressed following platinum-containing chemotherapy and who have had no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.16)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.</td>
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<td>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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. An FDA-approved test for the detection of MSI-H or dMMR is not currently available. (See Table 2)</td>
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<td>1.8 Gastric Cancer</td>
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<td>KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.</td>
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<td>KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1 or CPS &gt;13) as determined by an FDA-approved test [see Dosage and Administration (2.1)] and have disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. These indications are approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.9)]. Continued approval of these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.</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>Gastric Cancer</td>
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<td>First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric Cancer with Trastuzumab and Chemotherapy</td>
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<td>The safety analysis of Study KEYNOTE-811 included 217 patients with HER2-positive gastric cancer who received KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=186) or FP (n=29) every 3 weeks, compared to 216 patients who received placebo, trastuzumab, and CAPOX (n=187) or FP (n=29) every 3 weeks [see Clinical Studies (14.9)].</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.9 Gastric Cancer</td>
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<td>First-Line Treatment of Locally Advanced Gastric Cancer with HER2-Positive Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma</td>
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<td>The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811 (NCT03615336), a multicenter, randomized, double-blind, placebo-controlled trial that was designed to enroll 692 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥5 or CPS &gt;13), chemotherapy regimen (S-FU plus capecitabine [CAPOX] or S-FU plus cisplatin [FP]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World).</td>
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<td>Previously Treated Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma</td>
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<td>The efficacy of KEYTRUDA was investigated in KEYNOTE-059 (NCT02335411), a multicenter, nonrandomized, open-label multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy.</td>
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<td>14.10 Esophageal Cancer</td>
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<td>Previously Treated Locally Advanced or Metastatic Esophageal Cancer</td>
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<td>KEYNOTE-181</td>
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<td>The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease.</td>
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| 213736, 04/17/2020                     | Pemigatinib | Oncology | FGFR2 | Indication and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE
PEMAZYRE is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). |
| 010775, 05/10/2002                     | Perphenazine | Psychiatry | CYP2D6 | Precautions, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of locally advanced or metastatic cholangiocarcinoma with PEMAZYRE based on the presence of an FGFR2 fusion or rearrangement as detected by an FDA-approved test [see Clinical Studies (14.1)]. Information on FDA-approved test(s) for the detection of an FGFR2 fusion or rearrangement in cholangiocarcinoma is available at http://www.fda.gov/CompanionDiagnostics. |
| 125409, 01/16/2020                     | Pertuzumab (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies | 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)] • 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)]. |

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Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible. (…)

(…) The median age was 56 years (range: 26 to 77 years), 61% were female, 74% were White, and 95% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42%) or 1 (53%). Ninety-eight percent of patients had intrahepatic cholangiocarcinoma. Eighty-six percent of patients had in-frame FGFR2 gene fusions and the most commonly identified FGFR2 fusion was FGFR2-BICC1 (34%). Fourteen percent of patients had other FGFR2 rearrangements that could not be confidently predicted to be in-frame fusions, including rearrangements without an identifiable partner gene. All patients had received prior platinum-based therapy including 76% with prior gemcitabine/cisplatin.

(…) 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 had received prior platinum-based therapy including 76% with prior gemcitabine/cisplatin.

(…) The pharmacokinetics of perphenazine covary with the hydroxylation of debrisoquine which is mediated by cytochrome P450 2D6 (CYP 2D6) and thus is subject to genetic polymorphism - ie, 7%-10% of Caucasians and a low percentage of Asians have little or no activity and are called "poor" metabolizers. 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 had received prior platinum-based therapy including 76% with prior gemcitabine/cisplatin.

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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>. 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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| 125409, 01/16/2020 | Pertuzumab (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES
14.1 Metastatic Breast Cancer
CLEOPATRA (NCT00567196) was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. 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 were randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant therapy, chemotherapy, hormone therapy, or both) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant chemotherapy were required to have a disease-free interval of greater than 12 months before trial enrollment. (…)

14.2 Neoadjuvant Treatment of Breast Cancer
NeoSphere
NeoSphere (NCT00340088) was a multicenter, randomized, phase II trial conducted in 417 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 were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus docetaxel, or placebo plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. TRYPHAENA
An additional neoadjuvant study (TRYPHAENA, NCT00976989) was conducted in 425 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. 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. (…)

14.3 Adjuvant Treatment of Breast Cancer
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. (…)

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| 12.5 | Neurology | CYP2C9 | Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 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 (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. (…)
| 02/16/2021 | Phenytoin (1) | | | (…) Consistent results were observed across several patient subgroups including age (< 65 or ≥ 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 0.95 (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, 0.93). 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). (…)
| 008702, 02/16/2021 | | | | | |

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<td>Pharmacokinetics</td>
<td>12 CLINICAL</td>
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<td>Metabolism</td>
<td>PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Metabolism</td>
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**Pharmacogenomics**

- CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate or low levels of CYP2C9, may have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also result in decreased clearance of phenytoin (e.g., *2R, *6, *8, *11). The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2-3% in the white population, 5-4% in the Asian population, and <1% in the African American population. The CYP2D6*30 intermediate phenotype prevalence is approximately 35% in the white population, 24% in the African American population, and 15-36% in the Asian population.

**Warnings and Precautions**

- Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

**Clinical Pharmacology**

- Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

**Pharmacogenomic**

- In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

**Dosage and Administration**

- Reliable dose response data for the effects of ORAP (pimozide) on tic manifestation in Tourette’s Disorder patients below the age of twelve are not available.

**References**

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<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>At doses above 4 mg/day, CYP 2D6 genotyping should be performed. In poor CYP 2D6 metabolizers, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days (see Precautions – Pharmacogenomics).</td>
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</table>
| 018147, 05/03/2019                     | Piroxicam | Rheumatology | CYP2C9 | Clinical Pharmacology | **12 CLINOICAL PHARMACOLOGY**  
**12.3 Pharmacokinetics**  
Metabolism  
(…) Higher systemic exposure of piroxicam has been noted in subjects with CYP2C9 polymorphisms compared to normal metabolizer type subjects [see Clinical Pharmacology (12.5)].  
**12.5 Pharmacogenomics**  
CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/*2 (n=9), heterozygous CYP2C9*1/*3 (n=9), and homozygous CYP2C9*3/*3 (n=11) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/*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*1/*3 (n=9) and CYP2C9*3/*3 (n=11) genotypes were 1.7- and 8.8-fold higher than with subjects CYP2C9*1/*1 (n=17). It is estimated that the frequency of the homozygous*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.  
**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) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance. |
| 203469, 01/10/2020                     | Ponatinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | **1 INDICATIONS AND USAGE**  
Idusig (ponatinib) is a kinase inhibitor indicated for the:  
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.  
- Treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).  
**Limitations of use**  
Idusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML [see Warnings and Precautions (5.7)]. |

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<td>In the phase 2 trial, the incidence of venous thromboembolism was 9% (3/32) in patients with Ph+ ALL, 10% (6/62) in patients with blast phase (BP) CML, 4% (3/85) in patients with AP-CML, and 5% (13/270) in patients with CP-CML. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism [see Dosage and Administration (2.3)].</td>
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<td>5.4 Hepatotoxicity</td>
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<td>Iclusig can cause hepatotoxicity, including liver failure and death. Fulminating hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts. (…)</td>
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<td>5.10 Hemorrhage</td>
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<td>Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Iclusig in the phase 2 trial, with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subcutaneous hemorrhage were the most commonly reported serious bleeding events occurring in 1% (4/449) and 4/448, respectively. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia [see Warnings and Precautions (5.13)]. Interrupt Iclusig for serious or severe hemorrhage and evaluate [see Dosage and Administration (2.3)].</td>
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<td>5.13 Myelosuppression</td>
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<td>Myelosuppression was reported as an adverse reaction in 59% (260/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Iclusig. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (…)</td>
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<td>5.14 Tumor Lysis Syndrome</td>
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<td>Two patients (&lt;1%) treated with Iclusig developed serious tumor lysis syndrome. One case occurred in a patient with advanced APCML and one case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig.</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trial Experience</td>
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<td>Previously Treated CML or Ph+ ALL</td>
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<td>The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. (…) At the time of analysis (48 months of follow-up), 133 patients (30%) were ongoing (110 CP-CML; 20 AP-CML; 3 BP-CML; 0 Ph+ ALL), and the median duration of treatment with Iclusig was 22.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML, and 2.7 months in patients with Ph+ ALL. (…) The rates of treatment-emergent adverse reactions resulting in discontinuation were 19% in CP-CML, 12% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse reactions that led to treatment discontinuation was thrombocytopenia (4%). (See Table 5) (…) Laboratory Abnormalities</td>
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<td>(…) Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (See Table 7) (…)</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>One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (40%) as compared with patients &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 with patients &lt; 65 years of age (44%). (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>The safety and efficacy of Iclusig 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 Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML [Ph+ ALL]; resistance or intolerance [RI] 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 or progression to AP-CML or BP-CML at any time on prior TKI therapy. The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL).</td>
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</table>

* Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.
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<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>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 111). (…) 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 tisRTX 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 MHR 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 0.7 months (range: 0.4 to 5.5 months), respectively. The median duration of MHR for patients with AP-CML, BP-CML, and Ph+ ALL was 12.9 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+ months), respectively. 1 INDICATIONS AND USAGE GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). 1.2 RET-Mutant Medullary Thyroid Cancer GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). 1.3 RET Fusion-Positive Thyroid Cancer GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). 2 DOSE AND ADMINISTRATION 2.1 Patient Selection Select patients for treatment with GAVRETO based on the presence of a RET gene fusion (NSCLC or thyroid cancer) or RET gene mutation (MTC) [see Clinical Studies (14)]. Information on FDA-approved tests for RET gene fusion (NSCLC) is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. An FDA-approved test for the detection of RET gene fusion (thyroid cancer) and RET gene mutations is not currently available. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience The pooled safety population in the WARNINGS AND PRECAUTIONS reflects exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET altered solid tumors in ARROW [see Clinical Studies (14)]. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year. RET Fusion-Positive Non-Small Cell Lung Cancer The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW [see Clinical Studies (14)]. (…)Table 4 summarizes the adverse reactions in RET Fusion-Positive NSCLC Patients in ARROW. RET-altered Thyroid Cancer The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW [see Clinical Studies (14.2, 14.3)]. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year. (…) Table 6 summarizes the adverse reactions occurring in RET-altered Thyroid Cancer Patients in ARROW. 8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for RET-mutant MTC and RET-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of RET-mutant MTC and RET-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]. The safety and effectiveness of GAVRETO have not been established in pediatric patients with RET fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET-mutant MTC or RET-fusion thyroid cancer. 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics</td>
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<td>03/28/2019</td>
<td>Prasugrel (1)</td>
<td>Cardiology</td>
<td>CYP2C19 Use in Specific Populations, Clinical</td>
<td>8 USE IN SPECIFIC POPULATIONS</td>
<td>8.9 Metabolic Status</td>
</tr>
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</table>

Pralsetinib exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.
Cardioprotective strategies

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 fusionpositive 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 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 (OxTT). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. Patients received GAVRETO 400mg orally once daily until disease progression or unacceptable toxicity.

Metastatic RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 87 patients with RET fusion-positive NSCLC with measurable Disease who were previously treated with platinum chemotherapy enrolled into a cohort of ARROW. The median age was 60 years (range: 28 to 85); 49% were female, 53% were White, 35% were Asian, 6% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%), 99% of patients had metastatic disease, and 43% had either a history of or current CNS metastasis. Patients received a median of 2 prior systemic therapies (range 1-6); 45% had prior anti-PD1/PD-L1 therapy and 25% had prior kinase inhibitors. A total of 52% of the patients received prior radiation therapy. RET fusions were detected in 77% of patients using NGS (45% tumor samples; 26% blood or plasma samples, 6% unknown), 21% using FISH, and 2% using other methods. The most common RET fusion partners were KIF5B (70%) and CCDC6 (17%). Efficacy results for RET fusion-positive NSCLC who received prior platinum-based chemotherapy are summarized in Table 9. For the 59 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 89% (95% CI: 42, 74) and the median DOR was not reached (95% CI: 11.3, NE). No patients received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 8 patients including 2 patients with a CNS complete response; 75% of responders had a DOR of ≥ 6 months.

Treatment-naive RET Fusion-Positive NSCLC

Efficacy was evaluated in 27 patients with treatment-naive RET fusion-positive NSCLC with measurable disease enrolled into ARROW. The median age was 65 years (range 30 to 87); 52% were female, 59% were White, 33% were Asian, and 4% were Hispanic or Latino. ECOG performance status was 0-1 for 56% of the patients and all patients (100%) had metastatic disease 37% had either history of or current CNS metastasis. RET fusions were detected in 67% of patients using NGS (41% tumor samples; 22% blood or plasma; 4% unknown) and 33% using FISH. The most common RET fusion partners were KIF5B (70%) and CCDC6 (11%). Efficacy results for treatment-naive RET fusion-positive NSCLC are summarized in Table 9.

14.2 RET-Mutant Medullary Thyroid Cancer

The efficacy of GAVRETO was evaluated in patients with RET-mutant MTC in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with RET-mutant metastatic MTC previously treated with cabozantinib or vandetanib (or both). The median age was 59 years (range 30 to 85); 70% were male, 78% were White, 5% were Asian, 3% were Hispanic/Latino, 2% were Black, and 7% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-7). RET mutation status was detected in 73% using NGS (55% tumor sample, 18% plasma), 26% using PCR sequencing, and 2% other. The primary mutations in RET-mutant MTC previously treated with cabozantinib or vandetanib are described in Table 10. Efficacy results for RET-mutant MTC are summarized in Table 11.

Cabozantinib and Vandetanib-naive RET-mutant MTC

Efficacy was evaluated in 29 patients with RET-mutant advanced MTC who were cabozantinib and vandetanib treatment-naive. The median age was 61 years (range: 19 to 81); 72% were male, 76% were White, 17% were Asian, 3.4% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (5%), and 7% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-7). RET mutation status was detected in 90% using NGS (52% tumor sample, 35% plasma, 3.4% blood) and 10% using PCR sequencing. The primary mutations used to identify and enroll patients are described in Table 10. Efficacy results for cabozantinib and vandetanib-naive RET-mutant MTC are described in Table 10. Efficacy results for RET-mutant MTC are summarized in Table 11.

14.3 RET Fusion-Positive Thyroid Cancer

The efficacy of GAVRETO was evaluated in RET fusion-positive metastatic thyroid cancer patients in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). All patients with RET fusion-positive thyroid cancer were required to have disease progression following standard therapy, measurable disease by RECIST version 1.1, and have RET fusion status as detected by local testing (89% NGS tumor samples and 11% using FISH). The median age was 61 years (range: 46 to 74); 67% were male, 78% were White, 22% were Asian, 11% were Hispanic/Latino. All patients (100%) had papillary thyroid cancer. ECOG performance status was 0-1 (100%), all patients (100%) had metastatic disease, and 56% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-8). Prior systemic treatments included prior radioactive iodine (100%) and prior sorafenib and/or lenvatinib (56%). Efficacy results are summarized in Table 13.

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<td>022307, 03/28/2019</td>
<td>Prasugrel (2)</td>
<td>Cardiology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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. <strong>12 CLINICAL PHARMACOLOGY</strong> 12.5 Pharmacogenomics There is 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. <strong>14 CLINICAL STUDIES</strong> (...) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs 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>
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<td>022307, 03/28/2019</td>
<td>Prasugrel (3)</td>
<td>Cardiology</td>
<td>CYP3A5</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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. <strong>12 CLINICAL PHARMACOLOGY</strong> 12.5 Pharmacogenomics There is 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. <strong>14 CLINICAL STUDIES</strong> (...) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs 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>
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<td>Cardiology</td>
<td>CYP2B6</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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. <strong>12 CLINICAL PHARMACOLOGY</strong> 12.5 Pharmacogenomics There is 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. <strong>14 CLINICAL STUDIES</strong> (...) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs 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>
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<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Contraindications, Warnings, Precautions, Adverse</td>
<td><strong>CONTRAINDICATIONS</strong> Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings). <strong>WARNINGS</strong> Hemolytic anemia and G6PD deficiency</td>
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<td>Infectious Diseases</td>
<td>CYB5R</td>
<td>Precautions, Adverse Reactions</td>
<td>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).</td>
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<td>Rheumatology</td>
<td>G6PD</td>
<td>Adverse Reactions</td>
<td>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. OVERDOSE Symptoms of overdose 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.</td>
</tr>
<tr>
<td>020545</td>
<td>Procainamide</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>Adverse Reactions, Clinical Pharmacology</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<tr>
<td>021416, 11/02/2018</td>
<td>Propafenone</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>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 (7.3)]. 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 isozymes. 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, ...</td>
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<td>021438, 11/19/2013</td>
<td>Quinidine</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>rnitavir, 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.</td>
</tr>
<tr>
<td>073644, 07/17/2014</td>
<td>Propranolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>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 &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8 fold increase in plasma AUC of the TCA). (…) Constitutional deficiency of cytochrome P450 2D6 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 P450 2D6-dependent poor metabolizers from the major-phenotype &quot;extensive metabolizers&quot;. When drugs whose metabolism is P450 2D6-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 P450IID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphone and hydroxymorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers. Quinidine is not metabolized by cytochrome P450 2D6, but therapeutic serum levels of</td>
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<tr>
<td>089338, 02/02/2010</td>
<td>Propranolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>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 &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8 fold increase in plasma AUC of the TCA). (…) Constitutional deficiency of cytochrome P450 2D6 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 P450 2D6-dependent poor metabolizers from the major-phenotype &quot;extensive metabolizers&quot;. When drugs whose metabolism is P450 2D6-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 P450IID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphone and hydroxymorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers. Quinidine is not metabolized by cytochrome P450 2D6, but therapeutic serum levels of</td>
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| 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)

Quinine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. (…)
| 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) |
| 020815, 06/27/2018                    | Oncology | ESR (Hormone Receptor) | Clinical Studies | 14 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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<tr>
<td>02/2145, 03/05/2018</td>
<td>Raltegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>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 <em>28</em>/*28 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.</td>
</tr>
<tr>
<td>125477, 05/29/2020</td>
<td>Ramucirumab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 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.</td>
</tr>
<tr>
<td>125477, 05/29/2020</td>
<td>Ramucirumab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Non-Small Cell Lung Cancer RELAY The efficacy of CYRAMZA in combination with erlotinib was evaluated in RELAY (NCT02411448), a multinational, randomized, double-blind, placebo-controlled, multicenter study in patients with previously untreated metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Patients in RELAY were required to have measurable disease, ECOG PS of 0 or 1, no central nervous system (CNS) metastases, and no known EGFR T790M mutations at baseline. Patients were randomized (1:1) to receive either CYRAMZA 10 mg/kg or placebo every 2 weeks as an intravenous infusion, in combination with erlotinib 150 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (East Asia versus other), gender, EGFR mutation (exon 19 deletion versus exon 21 (L858R) substitution mutation), and local EGFR testing method (therascreen® and cobas® versus other polymerase chain reaction [PCR] and sequencing-based methods). A total of 449 patients were randomized, 224 to the CYRAMZA-treatment group and 225 to the placebo-treatment group. Baseline demographics and disease characteristics were similar between treatment arms. The median age was 65 years (range 23-89); 63% of patients were female; 77% were Asian and 22% were White; 52% had ECOG PS 0; 61% were never smokers; 54% had exon 19 mutation deletions, and 45% had exon 21 (L858R) substitution mutations. (…) REVEL (…) Tumor EGFR status was unknown for the majority of patients (65%). Where tumor EGFR status was known (n=445), 7.4% were positive for EGFR mutation (n=33). No data were collected regarding tumor ALK rearrangement status. (…)</td>
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| 103946, 12/12/2019                     | Rasburicase (1) | Oncology | G6PD | Boxed Warning, Contraindications, Warnings and Precautions | BOXED WARNING

WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

Hemolysis

Do not administer Elitek to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Elitek if hemolysis occurs. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek therapy (4, 5.2).

4 CONTRAINDICATIONS

Elitek is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) [see Boxed Warning, Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.2 Hemolysis

Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in <1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Boxed Warning, Contraindications (4)].

| 103946, 12/12/2007                     | Rasburicase (2) | Oncology | CYB5R | Boxed Warning, Contraindications, Warnings and Precautions | BOXED WARNING

WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

Methemoglobinemia

Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek if methemoglobinemia occurs (4, 5.3).

4 CONTRAINDICATIONS

Elitek is contraindicated in patients with a history of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase [see Boxed Warning, Warnings and Precautions (5)].

5 WARNINGS AND PRECAUTIONS

5.3 Methemoglobinemia

In clinical studies, methemoglobinemia occurred in <1% patients receiving Elitek. These included cases of serious hypoxemia requiring intervention with medical support measures. It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia. Immediately and permanently discontinue Elitek administration in any patient identified as having developed methemoglobinemia. Institute appropriate monitoring and support measures (e.g., transfusion support, metmyoglobinemia-blue administration) [see Boxed Warning, Contraindications (4)].

| 203085, 02/13/2020                     | Regorafenib | Oncology | RAS | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

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.

14 CLINICAL STUDIES

14.1 Colorectal Cancer

(…) 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 (6%). 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 bevacizumab. All but one patient with KRAS mutation/nondetectable tumors received panitumumab or cetuximab. (…)

| 200902, 01/21/2020                     | Ribociclib (1) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE

KISQALI is indicated in combination with:

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

• fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

6 ADVERSE REACTIONS

MONALEESA-2: KISQALI in combination with Letrozole

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

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. (…)

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| 209092, 01/21/2020 | Ribociclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | MONALEESA-7: KISQALI in combination with an Aromatase Inhibitor
Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a non-steroidal aromatase inhibitors (NSAI) or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. (…)
MONALEESA-3: KISQALI in combination with Fulvestrant
Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy
The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. (…)

14 CLINICAL STUDIES
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Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy
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MONALEESA-3: KISQALI in Combination with Fulvestrant
Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy
MONALEESA-3 was a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)

1 INDICATIONS AND USAGE
KISQALI is indicated in combination with:
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MONALEESA-3: KISQALI in Combination with Fulvestrant
Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy

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| 212728, 02/27/2020 Rimegepant | Anesthesiology | CYP2C9 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  | Other Specific Populations  
No clinically significant differences in the pharmacokinetics of rimegepant were observed based on age, sex, race/ethnicity, body weight, or CYP2C9 genotype (see Clinical Pharmacology (12.5)).  
12.5 Pharmacogenomics  
CYP2C9 activity is reduced in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Rimegepant Cmax and AUC0-inf were similar in CYP2C9 intermediate metabolizers (i.e., *1/*2, *2/*2, *1/*3, n=43) as compared to normal metabolizers (i.e., *1/*1, N=72). Adequate PK data are not available from CYP2C9 poor metabolizers (i.e., *2/*2). Since the contribution of CYP2C9 to rimegepant metabolism is considered minor, CYP2C9 polymorphism is not expected to significantly affect its exposure. |
| 213535, 08/07/2020 Risdiplam | Neurology | SMN1, SMN2 | Clinical Studies | 14 CLINICAL STUDIES  
(…) The median age of onset of clinical signs and symptoms of Type 1 SMA in patients enrolled in Part 1 of Study 1 was 2.0 months (range: 0.9 to 3.0); 71% of patients were female, 81% were Caucasian, and 19% were Asian. The median age at enrollment was 6.7 months (range: 3.3 to 6.9), and the median time between onset of symptoms and first dose was 4.0 months (range: 2.0 to 5.8). All patients had genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies. (…) |
| 020272, 01/25/2019 Risperidone | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  | Absorption  
Risperidone is well absorbed. The absolute oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution. Pharmacokinetic studies showed that RISPERDAL M-TAB Orally Disintegrating Tablets and RISPERDAL Oral Solution are bioequivalent to RISPERDAL Tablets.  
Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).  
Metabolism  
(…) CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers. Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone (see Drug Interactions (?)). This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given RISPERDAL do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone (see Drug Interactions (?)). 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 (?)). (…)  
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. |
| 103705, 03/13/2020 Rituximab | Oncology | MS4A1 (CD20 antigen) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific | 1 INDICATIONS AND USAGE 1.1 Non–Hodgkin’s Lymphoma (NHL)  
Rituxan (rituximab) is indicated for the treatment of patients with:  
• Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.  
• Relapsed or refractory, indolent or follicular lymphoma, 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-progression (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-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. |

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| 022406, 01/15/2019                     | Rivaroxaban | Cardiology | F5 (Factor V Leiden) | Clinical Studies | 1.2 Chronic Lymphocytic Leukemia (CLL)  
Rituxan (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.  
2 DOSAGE AND ADMINISTRATION  
2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)  
The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:  
- Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL  
  Administer once weekly for 4 or 8 doses.  
- Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL  
  Administer once weekly for 4 doses.  
- Previously Untreated, Follicular, CD20-Positive, B-Cell NHL  
  Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.  
- 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  
(…)
6.2 Post-marketing Experience  
F5 (Factor V Leiden)  
Populations, Clinical Studies  
(…)
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  
14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL  
The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in a single-arm study in 50 patients.  
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.  
14.3 Reduction in the Risk of Recurrence of DVT and/or PE  
EINSTEIN CHOICE Study  
(…)
14 CLINICAL STUDIES  
14.4 Non-progressing, Low-Grade, CD20-Positive, B-cell NHL  
(…)
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<th>020533, 11/02/2018</th>
<th>Ropivacaine (1)</th>
<th>Anesthesiology</th>
<th>G6PD</th>
<th>Warnings</th>
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<tbody>
<tr>
<td>020533, 11/02/2018</td>
<td>Ropivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
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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)].

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.

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLC01B1 521T>C). The frequency of this genotype (i.e., SLC01B1 521C/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.

Studies have demonstrated that the efficacy and safety of rosuvastatin are not affected by the CYP2C8*3 polymorphism, and CYP2C8*3 individuals and CYP2C8*3 heterozygotes benefited from treatment with rosuvastatin. However, the impact of the CYP2C19*2 polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established.

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

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<tr>
<td>021368, 11/09/2018</td>
<td>Rosuvastatin</td>
<td>Endocrinology</td>
<td>SLC01B1</td>
<td>Clinical Pharmacology</td>
<td>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.</td>
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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 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)].

Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy

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:


6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Treatment of BRCA-mutated Recurrent Ovarian Cancer After 2 or More Chemotherapies

(…) Rubraca 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 96), 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 Rubraca 600 mg twice daily was evaluated in a single arm trial (TRITON2) [see Clinical Studies (14.2)]. TRITON2 enrolled 209 patients with HRD-positive mCRPC, including 115 with BRCA-mutated mCRPC. Among the patients with BRCA-mutated mCRPC, the median duration of Rubraca treatment was 6.5 months (range 0.5 to 26.7). (…) 

Tables 6 and 7 summarize the adverse reactions and laboratory abnormalities, respectively, in patients with BRCA-mutated mCRPC in TRITON2. (See Tables 6 and 7) (…) 

14 CLINICAL STUDIES

14.1 Ovarian Cancer

Maintenance Treatment of Recurrent Ovarian Cancer

(…) Treatment of BRCA-mutated Recurrent Ovarian Cancer with Rubraca [see Clinical Studies (14.1)]. The median duration of Rubraca treatment was 6.5 months (range 0.5 to 26.7). (…) 

6.5 months (range 0.5 to 26.7). (…) 

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<tr>
<td><strong>209115, 05/15/2020</strong> Rucaparib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td><strong>12 CLINICAL PHARMACOLOGY</strong>&lt;br&gt;12.3 Pharmacokinetics&lt;br&gt;Specific Populations&lt;br&gt;CYP Enzyme Polymorphism</td>
<td>Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP Enzyme Polymorphism Specific Populations.</td>
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<tr>
<td><strong>209115, 05/15/2020</strong> Rucaparib (3)</td>
<td>Oncology</td>
<td>CYP1A2</td>
<td>Clinical Pharmacology</td>
<td><strong>12 CLINICAL PHARMACOLOGY</strong>&lt;br&gt;12.3 Pharmacokinetics&lt;br&gt;Specific Populations&lt;br&gt;CYP Enzyme Polymorphism</td>
<td>Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP1A2 or CYP Enzyme Polymorphism Specific Populations.</td>
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<tr>
<td><strong>209115, 05/15/2020</strong> Rucaparib (4)</td>
<td>Oncology</td>
<td>BRCA Loss of Heterozygosity (Homologous Recombination Deficiency)</td>
<td>Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td><strong>5 WARNINGS AND PRECAUTIONS</strong>&lt;br&gt;5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia&lt;br&gt;Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur in patients treated with Rubraca, and are potentially fatal adverse reactions. In 1146 treated patients [see Adverse Reactions (6.1)], MDS/AML occurred in 20 patients (1.7%), including those in long term follow-up. Of these, 8 occurred during treatment or during the 28 day safety follow-up (0.7%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 53 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or other DNA damaging agents.</td>
<td>&lt;br&gt;<strong>6 ADVERSE REACTIONS</strong>&lt;br&gt;6.1 Clinical Trials Experience&lt;br&gt;Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy</td>
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<tr>
<td>761115, 04/22/2020</td>
<td>Selpercatinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
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<td>1.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer</td>
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<td>RETEVIMO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC). This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).</td>
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<td>1.2 RET-Mutant Medullary Thyroid Cancer</td>
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<td>Neurology</td>
<td>AQP4</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.5 Use in Patients with Reduced UGT1A1 Activity</td>
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<td>Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)<em>28 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 UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (103/391) in patients homozygous for the UGT1A1</em>28 allele, 13% (20/155) in patients heterozygous for the UGT1A1<em>28 allele and 11% (16/146) in patients homozygous for the wild-type allele [see Clinical Pharmacology (12.5)]. Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1</em>28 is not known and should be considered based on individual patient tolerance to treatment [see Dosage and Administration (3.3)].</td>
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The efficacy of RETEVMO was evaluated in patients with RET-mutant MTC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic RET-mutant MTC who had previously been treated with cabozantinib or vandetanib (or both) and patients with advanced or metastatic RET-mutant MTC who were naïve to cabozantinib and vandetanib in separate cohorts. RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with RET-mutant advanced MTC who had previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.

The median age was 57 years (range: 17 to 84); 66% were male; 89% were White; 7% were Hispanic/Latino, and 1.8% were Black. ECOG performance status was 0 (62%), 1 (18%) and 2 (8%). 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 – 8). RET mutation status was detected in 82% of patients using NGS (78% tumor samples; 4% blood or plasma), 16% using PCR, and 2% using an unknown test. The protocol excluded patients with synchronous, frameshift or nonsense RET mutations; the specific mutations used to identify and enroll patients are described in Table 10. (See Table 10)

Efficacy results for RET-mutant MTC are summarized in Table 11. (See Table 11)

Caboza.ond and Vandetanib-naive RET-Mutant MTC

Efficacy was evaluated in 88 patients with RET-mutant MTC who were cabozantinib and vandetanib treatment-naive enrolled into a cohort of LIBRETTO-001. The median age was 58 years (range: 15 to 82) with two patients (2.3%) aged 12 to 16 years; 66% were male; and 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3.4%). All patients (100%) had metastatic disease and 18% had received 1 or 2 prior systemic therapies (including 8% kinase inhibitors, 4.5% chemotherapeutic, 2.3% anti-PD1/PD-L1 therapy, and 1.1% radioactive iodine). RET mutation status was detected in 76.4% of patients using NGS (76.1% tumor samples; 2.3% blood samples), 18.2% using PCR, and 3.4% using an unknown test. The mutations used to identify and enroll patients are described in Table 10. (See Table 10)

Efficacy results for cabozantinib and vandetanib-naive RET-mutant MTC are summarized in Table 12. (See Table 12)

14.3 RET Fusion-Positive Thyroid Cancer

The efficacy of RETEVMO was evaluated in patients with advanced RET fusion-positive thyroid cancer enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 27 patients with RET fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients with RET fusion-positive thyroid cancer who were RAI-refractory and had received sorafenib, lenvatinib, or both, in separate cohorts.

The median age was 54 years (range: 20 to 88); 52% were male; 74% were White, 11% were Hispanic/Latino, 7.4% were Asian, and 3.7% were Black. ECOG performance status was 0-1 (89%) or 2 (11%). (All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (78%), poorly differentiated thyroid cancer (11%), anaplastic thyroid cancer (7%), and Hurthle cell thyroid cancer (4%). Patients had received a median of 3 prior therapies (range 1–7). RET fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using blood samples. Efficacy results for RET fusion-negative thyroid cancer are summarized in Table 13. (See Table 13)

WARNINGs

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 nyanodine 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, hypercapnia, and hypovolemia.

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.

Treatment of malignant hyperthermia includes discontinuation of triggering agents (e.g., sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), and application of supportive therapy. Supportive therapy may include efforts to restore body temperature, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

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| 213793, 11/25/2020                      | Setmelanotide (2) | Endocrinology | PCSK1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 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 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, PCSK1, or LEPR 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)  
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 39% screened negative. The 61% of patients who screened positive for antibodies to IMCIVREE were inconclusive for antibodies to IMCIVREE in the confirmatory assay. There was no observation of a rapid decline in IMCIVREE concentrations to suggest the presence of anti-drug antibodies. (…) Approximately 13% of adult and pediatric patients with LEPR deficiency (3 patients) confirmed positive for antibodies to alpha-MSH that were classified as low-titer and non-persistent. Of these 3 patients (13%), 2 tested positive post-IMCIVREE treatment and 1 was positive pretreatment. None of the patients with POMC-deficiency were confirmed to have antibodies to alpha-MSH. (…)  
8 USE IN SPECIFIC POPULATIONS  
8.4 Pediatric Use  
The safety and effectiveness of IMCIVREE have 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 33.0 kg/m². Weight in pediatric patients was 95th percentile using growth chart assessments.  
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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. **Clinical Studies**

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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). 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 (polygenic) obesity

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)].

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 39% screened negative. The 61% of patients who screened positive for antibodies to IMCIVREE were incoclusive 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 or 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. (…)
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<td>Simeprevir</td>
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<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs1297980) is a C [cytosine] to T [thymine] substitution is a strong predictor of response to Peg-IFN-α and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor. Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with OLYSIO-containing regimens. (See Table 12 and 13)</td>
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14 CLINICAL STUDIES
14.2 OLYSIO in Combination with Sofosbuvir Adult Subjects with HCV Genotype 1 Infection (…) These 59 subjects had a median age of 45 years (range 27 to 68 years; with 2% above 65 years); 56% were male; 19% were White, 26% Black or African American, 19% Hispanic; 36% of which were enrolled in China and 19% in South Korea); 53% had a body mass index (BMI) greater than or equal to 30 kg/m²; 85% had baseline HCV RNA levels greater than 800000 IU/mL; 75% had HCV genotype 1a of which 40% had Q80K polymorphism at baseline, and 99% had IL28B CC genotype, 5% IL28B CT genotype, and 1% IL28B TT genotype; 7% had prior null responders to Peg-IFN-α and RBV, and 26% were treatment-naïve. OPTIMIST-1 was an open-label, randomized Phase 3 trial in HCV genotype 1-infected subjects without cirrhosis who were treatment-naïve or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred fifty-five subjects received 12 weeks of OLYSIO with sofosbuvir. The 155 subjects without cirrhosis receiving 12 weeks of OLYSIO with sofosbuvir had a median age of 56 years (range 18 to 68 years; with 2% above 65 years); 49% were male; 81% were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater than or equal to 30 kg/m²; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 72% had METAVIR fibrosis scores F0-F3, F2 and F3, respectively, and 29% had 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; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-α-2a; in QUEST 2, 69% of the subjects received Peg-IFN-α-2a and 31% received Peg-IFN-α-2b. Table 17 shows the response rates in treatment-naïve adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR12 rates were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. (See Table 17) (…) Treatment-Naïve East Asian Subjects with HCV Genotype 1 Infection (…) These 304 subjects had a median age of 45 years (range 18 to 68 years; with 2% above 65 years); 49% were male; all were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater than or equal to 30 kg/m²; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 75% had HCV genotype 1a of which 41% carried Q80K at baseline, 14% had HCV genotype 1b; 14% had IL28B CC genotype, 22% IL28B TT genotype; 75% were prior null responders to Peg-IFN-α and RBV, and 26% were treatment-naïve. OPTIMIST-1 was an open-label, randomized Phase 3 trial in HCV genotype 1-infected subjects without cirrhosis who were treatment-naïve or treatment-experienced (including prior relearners, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred fifty-five subjects received 12 weeks of OLYSIO with sofosbuvir. The 155 subjects without cirrhosis receiving 12 weeks of OLYSIO with sofosbuvir had a median age of 56 years (range 18 to 68 years; with 2% above 65 years); 49% were male; 81% were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater than or equal to 30 kg/m²; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 75% had HCV genotype 1a of which 40% had Q80K polymorphism at baseline, and 26% had HCV genotype 1b; 26% had IL28B CC genotype, 55% IL28B CT genotype, and 17% IL28B TT genotype; 74% were treatment-naïve 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 subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1a (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-α and RBV Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection (…) In the pooled analysis of 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 2% Hispanic; 28% had IL28B CC genotype, 55% IL28B CT genotype, and 17% IL28B TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-α-2a; in QUEST 2, 69% of the subjects received Peg-IFN-α-2a and 31% received Peg-IFN-α-2b. Table 17 shows the response rates in treatment-naïve adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR12 rates were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. 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| Siponimod                              | Neurology | CYP2C9 | Dosage and Administration, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 2.1 Assessments Prior to First Dose of MAYZENT | Before initiation of treatment with MAYZENT, assess the following: 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 titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 2 mg taken orally once daily starting on Day 0. Dosage adjustment is required in patients with a CYP2C9 *1/*3 or *2/*3 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 1-mg maintenance dosage (see How Supplied/Storage and Handling (16.1, 16.2)). (See Table 1)
If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

2.3 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3 Maintenance Dosage
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.

4 CONTRAINDICATIONS
MAYZENT is contraindicated in patients who have:
• A CYP2C9*3/*3 genotype (see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)) (…)

7 DRUG INTERACTIONS
7.6 CYP2C9 and CYP3A4 Inducers
Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer. Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.
Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and*2/*3 genotype (see Clinical Pharmacology (12.3)).

8 USE IN SPECIFIC POPULATIONS
8.6 CYP2C9 Genotype

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Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%–0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or*2/*3 genotype because of an increase in exposure to siponimod [see Dosage and Administration (2.3) and Clinical Pharmacology (12.5)].

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

**Immune System**

MAYZENT induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, caused by the reversible sequestration of lymphocytes in lymphoid tissues.

With continued daily dosing, the lymphocyte count continues to decrease, reaching a nadir median (90% CI) lymphocyte count of approximately 0.560 (0.271-1.08) cells/µL in a typical CYP2C9*1/*1 or *1/*2, non-Japanese patient, corresponding to 20% to 30% of baseline. Low lymphocyte counts are maintained with chronic daily dosing [see Warnings and Precautions (5.1)].

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. After stopping MAYZENT treatment, residual lowering effects on peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose [see Warnings and Precautions (5.1)].

12.3 Pharmacokinetics

**Drug Interaction Studies**

Siponimod as an Object of Interaction

CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. Physiologically based PK modeling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated.

Coadministration of Siponimod with CYP2C9 and CYP3A4 Inhibitors

The coadministration of fluconazole (moderate CYP2C9 and CYP3A4 dual inhibitor) 200 mg daily at steady-state and a single dose of siponimod 4 mg in CYP2C9*1/*1 healthy volunteers led to a 2-fold increase in the AUC of siponimod. Mean siponimod terminal half-life was increased by 50%. Fluconazole led to a 2- to 4-fold increase in the AUC,tau,ss of siponimod across different CYP2C9 genotypes, according to in silico evaluation [see Drug Interactions (7.3)].

Coadministration of Siponimod with CYP2C9 and CYP3A4 Inducers

The coadministration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampin (strong CYP3A4 and moderate CYP2C9 dual inducer) decreased siponimod AUC,tau,ss and Cmax,ss by 57% and 45%, respectively in CYP2C9*1/*1 subjects. Rifampin and efavirenz (moderate CYP3A4 inducer) reduced the AUC,tau,ss of siponimod by up to 78% and up to 52%, respectively, across CYP2C9 genotypes, according to in silico evaluation [see Drug Interactions (7.6)].

**Oral Contraceptives**

The effects of coadministration of siponimod 2 mg and 4 mg (twice the recommended dosage) once daily with a monophasic oral contraceptive (OC) containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were assessed in 24 healthy female subjects (18 to 40 years of age; CYP2C9*1/*1 genotype). There were no clinically relevant effects on the PK or PD of the OC. No interaction studies have been performed with OCs containing other progestagens; however, an effect of siponimod on their exposure is expected. 12.5 Pharmacogenomics

The CYP2C9 genotype has a significant impact on siponimod metabolism. After a single dose of 0.25 mg siponimod, AUC,inf and AUC, last was approximately 2- to 4-fold higher in CYP2C9*2/*2 and CYP2C9*3/*3 genotypes, respectively, while there was only a minor increase of Cmax by 21% and 16%, respectively, compared to extensive metabolizers (CYP2C9*1/*1). Mean half-life is prolonged in CYP2C9*2/*3 and CYP2C9*3/*3 subjects, respectively, compared to CYP2C9*1/*1 subjects [see Dosage and Administration (2.3) and Contraindications (5.1)].

An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9*1/*1 and CYP2C9*3/*3) MS 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*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 genotypes, respectively. The resulting increase in siponimod AUC was approximately 25, 61, 91, and 285% higher in CYP2C9*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 subjects, respectively, as compared to CYP2C9*1/*1 subjects [see Dosage and Administration (2.1, 2.3) and Contraindications (4)]. As the apparent clearance estimated for CYP2C9*2/*2 subjects is comparable to that of CYP2C9*1/*1 subjects, similar siponimod exposure is expected for both genotypes.

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<td>021196, 09/25/2020</td>
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<td>ALDH5A1</td>
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<td>Inborn Errors of Metabolism</td>
<td>ASS1, CPS1, OTC (Urea Cycle Disorders)</td>
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</table>

#### 5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

Sodium nitrite has been associated with severe hypotension, methemoglobinemia, and death at doses less than twice recommended therapeutic doses. Hypotension may occur concurrently or separately. Sodium nitrite should be used to treat life-threatening cyanide poisoning. When the diagnosis of cyanide poisoning is uncertain and/or the patient is not in extremis, special consideration should be given to administration of sodium nitrite if the patient is known or suspected to have diminished oxygen or cardiovascular reserve (e.g., smoke inhalation victims, pre-existing anemia, substantial blood loss, cardiac or respiratory compromise) or to be at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency).

5.2 Methemoglobinemia

Supportive care alone may be sufficient treatment without administration of antidotes for many cases of cyanide intoxication, particularly in conscious patients without signs of severe toxicity. Monitor patients closely to ensure adequate perfusion and oxygenation during treatment with sodium nitrite.

Monitor methemoglobin levels and administer oxygen during treatment with sodium nitrite whenever possible. When sodium nitrite is administered to humans a wide range of methemoglobin concentrations occur.

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| 11/09/2017 | 209195, 11/09/2017 | Sofosbuvir, Velpatasvir, and Voxlaptavir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | ‡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% (27/38). (See Table 9) 14.2 Clinical Trials in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis Genotype 1, 2, 4, 5, and 6 HCV Infected Adults (ASTRAL-1) (…) 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 male; 79% were White; 9% were Black; 21% had a baseline body mass index at least 30 kg/m2; the proportions of subjects with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5%, and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced. (…) Genotype 2 HCV Infected Adults (ASTRAL-2) (…) Demographics and baseline characteristics were balanced across the two treatment groups. Of the 286 treated subjects, the median age was 59 years (range: 23 to 81); 59% of the subjects were male; 88% were White; 7% were Black; 33% had a baseline body mass index at least 30 kg/m2; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels at least 800,000 IU/mL; 14% had compensated cirrhosis; and 15% were treatment-experienced. (…) Genotype 3 HCV Infected Adults (ASTRAL-3) (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 552 treated subjects, the median age was 52 years (range: 19 to 76); 62% of the subjects were male; 89% were White; 9% were Asian; 20% had a baseline body mass index at least 30 kg/m2; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels at least 800,000 IU/mL; 30% had compensated cirrhosis; and 26% were treatment-experienced. (…) 14.3 Clinical Trial in Subjects Coinfected with HCV and HIV-1 (…) Demographics and baseline characteristics were balanced across the two treatment groups. Of the 552 treated subjects, the median age was 52 years (range: 19 to 76); 62% of the subjects were male; 89% were White; 9% were Asian; 20% had a baseline body mass index at least 30 kg/m2; the proportions of subjects with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5%, and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced. (…) Genotype 2 HCV Infected Adults (ASTRAL-2) (…) Demographics and baseline characteristics were balanced across the two treatment groups. 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(…) 14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1 (…) 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 accounting 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. (…) 14.5 Clinical Trial in Pediatrics 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)) 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 81 kg (range: 30 to 101 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 800,000 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. The SVR12 rate was 100% (13/13) in genotype 2 subjects and 97% (36/37) in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse.

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<td>Sotirasib</td>
<td>Oncology</td>
<td>KRAS</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>LUMAKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test (see Dosage and Administration [2.1]), who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).</td>
</tr>
</tbody>
</table>

1 INDICATIONS AND USAGE
LUMAKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test (see Dosage and Administration [2.1]), who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for treatment of locally advanced or metastatic NSCLC with LUMAKRAS based on the presence of KRAS G12C mutation in tumor 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 KRAS G12C mutations is available at: http://www.fda.gov/CompanionDiagnostics.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to LUMAKRAS as a single agent at 960 mg orally once daily in 357 patients in with NSCLC and other solid tumors with KRAS G12C mutation enrolled in CodeBreaK 100, 28% were exposed for 6 months or longer and 3% were exposed for greater than one year.

Non-Small Cell Lung Cancer
The safety of LUMAKRAS was evaluated in a subset of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC in CodeBreaK 100 [see Clinical Studies (14)]. Patients received LUMAKRAS 960 mg orally once daily until disease progression or unacceptable toxicity (n = 204). Among patients who received LUMAKRAS, 39% were exposed for 6 months or longer and 3% were exposed for greater than one year. (See Tables 3 and 4) (…)

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
The pharmacokinetics of sotorasib have been characterized in healthy subjects and in patients with KRAS G12C-mutated solid tumors, including NSCLC. Sotorasib exhibited non-linear, time-dependent, pharmacokinetics over the dose range of 180 mg to 960 mg (0.19 to 1 time the approved recommended dosage) once daily with similar systemic exposure (i.e., AUC(0-24h) and Cmax) across doses at steady-state. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets predosed in water administered under fasted conditions. Sotorasib plasma concentrations reached steady state within 22 days. No accumulation was observed after repeat LUMAKRAS dosages with a mean accumulation ratio of 0.56 (coefficient of variation (CV): 59%).

14 CLINICAL STUDIES
The efficacy of LUMAKRAS was demonstrated in a subset of patients enrolled in a single-arm, open-label, multicenter trial (CodeBreaK 100 [NCT03600883]). Eligible patients with KRAS G12C-mutated NSCLC with disease progression after receiving an immune checkpoint inhibitor and/or platinum-based chemotherapy, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

All patients were required to have prospectively identified KRAS G12C-mutated NSCLC in tumor tissue samples by using the QIAGEN therascreen® KRAS RQG PCR Kit performed in a central laboratory. Of 126 total enrolled subjects, 2 (2%) were unevaluable for efficacy analysis due to the absence of tumor tissue samples. Of the 124 patients with KRAS G12C mutations confirmed in tumor tissue, plasma samples from 112 patients were tested retrospectively using the Guardant360® CDx. 78/112 patients (70%) had KRAS G12C mutation identified in plasma specimen, 31/112 patients (28%) did not have KRAS G12C mutation identified in plasma specimen and 3/112 (2%) were unevaluable due to Guardant360® CDx test failure. (See Table 5)

019998, 10/02/2018 | Succimer | Hematology | G6PD | 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-phosphodehydrogenase (G6PD) deficiency without adverse reactions. (…)

008453, 07/26/2018 | Succinylcholine (1) | Anesthesiology | BCHE | Warnings, Precautions | WARNINGS
(…) Succinylcholine 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.

PRECAUTIONS
Reduced Plasma Cholinesterase Activity
Succinylcholine should be used carefully in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. The likelihood of prolonged neuromuscular block following administration of succinylcholine must be considered in such patients (see DOSAGE AND ADMINISTRATION). Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for atypical plasma cholinesterase gene), pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. (…)

(…) Patients homozygous for atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine. In these patients, a 5- to 10-mg test dose of succinylcholine may be administered to evaluate sensitivity to succinylcholine, or neuromuscular blockade may be produced by the cautious administration of a 1-mg/ml solution of succinylcholine by slow IV infusion. Apnea or prolonged muscle paralysis should be treated with controlled respiration.

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<td>008453, 07/26/2018</td>
<td>Succinylcholine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Boxed Warning, Contraindications, Warnings, Precautions, Adverse Reactions</td>
<td>WARNING RISK OF CARDIAC ARREST FROM HYPERKALEMIC Rhabdomyolysis</td>
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<td>There have been rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death after the administration of succinylcholine 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 in 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 succinylcholine 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, with hyperventilation. 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, 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 succinylcholine 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.</td>
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<td>017381, 04/30/2016</td>
<td>Sulfadiazine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNING (…) The use of SILVADENE Cream 1% (silver sulfadiazine) in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur.</td>
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<td>PRECAUTIONS Hemolysis In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see Clinical Pharmacology and Dosage and Administration).</td>
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<tr>
<td>017377, 04/30/2021</td>
<td>Sulfamethoxazole and Trimethoprim (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Electrolyte Abnormalities (…) During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are &quot;slow acetylators&quot; may be more prone to idiosyncratic reactions to sulfonamides, (…)</td>
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<tr>
<td>017377, 04/30/2021</td>
<td>Sulfamethoxazole and Trimethoprim (2)</td>
<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Precautions</td>
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<td>007073, 04/30/2021</td>
<td>Sulfasalazine (1)</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Precautions</td>
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| 03/04/2014 | Sulfasalazine (2) | Gastroenterology | Nonspecific (NAT) | Clinical Pharmacology | **CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

Metabolism: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to 5-hydroxy sulfapyridine (SPOH) and N-acetyl-5-hydroxy sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a nonacetylation phenotype-dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible.

**Special Populations**

Acetylator Status: The metabolism of SP to AcSP is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life 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; 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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<th>02/0992, 11/30/2020</th>
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<th>Gynecology</th>
<th>PROC</th>
<th>Contraindications</th>
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<th>02/0992, 11/30/2020</th>
<th>Synthetic Conjugated Estrogens, A (3)</th>
<th>Gynecology</th>
<th>SERPINC1 (Antithrombin III)</th>
<th>Contraindications</th>
</tr>
</thead>
</table>

| 21/1996, 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**

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<tbody>
<tr>
<td>210607, 08/08/2018</td>
<td>Tafenoquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>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)</td>
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</tbody>
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<tbody>
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<td>211651, 03/09/2020</td>
<td>Talazoparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Selected patients for therapy based on an FDA-approved companion diagnostic for TALZENNA [see Dosage and Administration (2.1)].</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>211651, 03/09/2020</td>
<td>Talazoparib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Selected patients for therapy based on an FDA-approved companion diagnostic for TALZENNA [see Dosage and Administration (2.1)].</td>
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<td>021807, 04/08/2019</td>
<td>Tamoxifen (1)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Metastatic Breast Cancer SOLTAMOX is indicated for the treatment of adult patients with estrogen receptor-positive metastatic breast cancer. 1.2 Adjuvant Treatment of Breast Cancer SOLTAMOX is indicated:  † for the adjuvant treatment of adult patients with early stage estrogen receptor-positive breast cancer  † to reduce the occurrence of contralateral breast cancer in adult patients when used as adjuvant therapy for the treatment of breast cancer. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience 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 33 months, the combination of anastrozole and tamoxifen did not demonstrate an efficacy benefit when compared to tamoxifen monotherapy in all patients as well as in the hormone receptor-positive subgroup. The combination treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving 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 WHEL (Women’s Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p&lt;0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers. 14 CLINICAL STUDIES 14.2 Adjuvant Treatment of Breast Cancer The Early Breast Cancer Trials Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, 1995, 1998 and 2011. The 10-year outcome data were reported in 1998 for 36,689 women in 55 randomized trials of another formulation of adjuvant tamoxifen using doses of 20 to 40 mg per day for 1 to 5+ years. Twenty-five percent of patients received 1 year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Forty-eight percent of tumors were estrogen receptor (ER)-positive (&gt;10 fmol/mg), 21% were ER-poor (&lt;10 fmol/mg), and 31% were ER-unknown. Among 29,441 patients with ER-positive or ER-unknown breast cancer, 58% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node-positive disease and 46% had node-negative disease. In women with ER-positive or ER-unknown breast cancer:  † with positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for tamoxifen vs. 50.5% for control (log-rank 2p &lt; 0.00001). The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (log-rank 2p &lt; 0.00001).  † with negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (log-rank 2p &lt; 0.00001). The recurrence-free rate at 10 years was 78.2% for tamoxifen vs. 64.3% for control (log-rank 2p &lt; 0.00001).  † who received 1 year or less, 2 years, or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17%, and 26%, respectively (2p &lt; 0.003). The corresponding reductions in breast cancer recurrence were 21%, 29%, and 47% (2p &lt; 0.00001). Results in patients with ER-poor breast cancer  † Benefit is less clear for women with ER-poor breast cancer in whom the proportional reduction in recurrence was 10% (2p = 0.007) for all durations taken together, or 9% (2p = 0.02) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (not significant). Node-positive: Individual Studies  (...) In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50 to 59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while survival results were poorer in women in whom both estrogen and progesterone receptor levels less than 10 fmol. In women age 60 to 70 years, there was an improvement in disease-free survival with tamoxifen without any clear relationship to estrogen or progesterone receptor status. (...) Node-negative: Individual Studies NSABP B-14, a prospective, double-blind, randomized study, compared another formulation of tamoxifen to placebo as adjuvant therapy in women with axillary node-negative, estrogen-receptor positive (≥20 fmol/mg cytosol protein) breast cancer (following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50. One additional randomized study (NATO) demonstrated improved disease-free survival for another formulation of tamoxifen compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of tamoxifen appeared to be independent of estrogen receptor status.</td>
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<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.2 Thromboembolic Events</td>
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<td>021807, 04/08/2019</td>
<td>Tamoxifen (3)</td>
<td>Oncology</td>
<td>F2 (Prothrombin)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>021807, 04/08/2019</td>
<td>Tamoxifen (4)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Metabolism</td>
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<td>Tamoxifen is extensively metabolized by CYP450 enzymes, including CYP3A, CYP2D6, CYP2C9, CYP2C19, and CYP2B6. N-desmethyltamoxifen, formed predominantly by CYP3A, is the major metabolite found in plasma. The pharmacological activity of N-desmethyltamoxifen is similar to that of tamoxifen. Endoxifen and 4-hydroxytamoxifen, identified as minor metabolites, have 100-fold greater affinity for the estrogen receptor and 30 to 100-fold greater potency in suppressing estrogen-dependent cell proliferation than tamoxifen. The polymorphic enzyme CYP2D6 is involved in the formation of endoxifen and 4-hydroxytamoxifen, and it is the key enzyme that catalyzes the formation of endoxifen from N-desmethyltamoxifen. Endoxifen concentrations may differ among patients because of various CYP2D6 genotypes (see Clinical Pharmacology (12.5)). Phase 2 enzymes, such as SULT1A1, UGT2B7, and UGT1A4, are associated with tamoxifen clearance from plasma.</td>
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<td>12.5 Pharmacogenomics</td>
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<td>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 and Eating) Study (NCT00037878), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.8 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p&lt;0.0001). 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>020579, 01/23/2019</td>
<td>Tamsulosin</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Adverse Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.2 Drug Interactions</td>
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<td>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., terfenadine) inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers particularly at a dose higher than 0.4 mg (e.g., 0.8 mg) (see Drug Interactions (7.1) and Clinical Pharmacology (12.3)).</td>
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<td>7 DRUG INTERACTIONS</td>
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<td>Tamsulosin 0.4 mg (as a component of FLOMAX) is contraindicated in patients who are CYP2D6 poor metabolizers (PM) as defined by their CYP2D6 phenotype, because of the risk of a potentially lethal interaction with other CYP2D6 substrates (e.g., terfenadine, astemizole). The recommendation applies only to CYP2D6 PMs.</td>
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| 201917, 10/23/2013                     | Telaprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology, Clinical Studies | The efficacy of TELAPREVIR was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring MET exon 14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. (…)

14 CLINICAL STUDIES
14.2 Treatment-Naïve Adults
Trial C211 (OPTIMIZE) (…) SVR rates were similar for the T12 (twice daily)/PR and T12 (q8h)/PR groups across subgroups determined by sex, age, race, ethnicity, body mass index, HCV genotype subtype, IL28B genotype, baseline HCV RNA (less than 800,000, greater than or equal to 800,000 IU per mL), and extent of liver fibrosis. However, there were small numbers of subjects enrolled in some key subgroups. (…)

02/03/2021, 214096 | Tepotinib (1) | Oncology | ALK | Clinical Studies | The efficacy of TEPOTINIB was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring MET exon 14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. (…)

02/03/2021, 214096 | Tepotinib (2) | Oncology | EGFR | Clinical Studies | The efficacy of TEPOTINIB was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring MET exon 14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. (…)

02/03/2021, 214096 | Tepotinib (3) | Oncology | MET | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | TEPOTINIB is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection for METex14 Skipping Alterations
Select patients for treatment with TEPOTINIB on the basis of the MET exon 14 skipping alterations in plasma or tumor specimens. Testing for the presence of MET exon 14 skipping alterations in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If an alteration is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. An FDA-approved test for detection of MET exon 14 skipping alterations in NSCLC for selecting patients for treatment with TEPOTINIB is not available.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to TEPOTINIB in 448 patients with solid tumors enrolled in five open-label, single-arm studies receiving TEPOTINIB as single agent at a dose of 450 mg once daily. This included 255 patients with NSCLC positive for MET exon 14 skipping alterations.

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| 021894, 09/13/2017                     | Tetrabenazine | Neurology | CYP2D6 | Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | METEx14 skipping alterations, who received TEPMETKO in VISION. Among 448 patients who received TEPMETKO, 32% were exposed for 6 months or longer, and 12% were exposed for greater than one year. The data described below reflect exposure to TEPMETKO 450 mg once daily in 255 patients with metastatic non-small cell lung cancer (NSCLC) with METEx14 skipping alterations in VISION [see Clinical Studies (14)]. (See Table 2) (…)

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use
Of 255 patients with METEx14 skipping alterations in VISION who received 450 mg TEMETKO once daily, 79% were 65 years or older, and 43% were 75 years or older. No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients.

14 CLINICAL STUDIES
The efficacy of TEPMETKO was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring METEx14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. Identification of METEx14 skipping alterations was prospectively determined using central laboratories employing either a PCR-based or next-generation sequencing-based clinical trial assay using tissue (58%) and/or plasma (65%) samples. (…)

2 DOSAGE AND ADMINISTRATION
2.2 Individualization of Dose
Dosing Recommendations Above 50 mg per day
Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as PMs or EMs [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

Extensive and Intermediate CYP2D6 Metabolizers
Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse reactions such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antipsychotics) [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

Poor CYP2D6 Metabolizers
In PMs, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

5 WARNINGS AND PRECAUTIONS
5.3 Laboratory Tests
Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are poor metabolizers (PMs), extensive (EMs) or intermediate metabolizers (IMs) of XENAZINE.

Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient’s CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg [see Dosage and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS
8.7 Poor or Extensive CYP2D6 Metabolizers
Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

Poor Metabolizers
Poor CYP2D6 metabolizers (PM) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) compared to EMs. The dosage should, therefore, be adjusted according to a patient’s CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

Extensive / Intermediate Metabolizers
In extensive (EMs) or intermediate metabolizers (IMs), the dosage of XENAZINE can be titrated to a maximum single dose of 37.5 mg and a recommended maximum daily dose of 100 mg [see Dosage and Administration (2.2), Drug Interactions (7.1), Clinical Pharmacology (12.3)].

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<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 Thioguanine (2) 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>CYP2C19</td>
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<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
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<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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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. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency was 1.5-2.5 mg/kg (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%.

**1 INDICATIONS AND USAGE**

1.1 Metastatic Colorectal Cancer

LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, and either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

Metastatic Gastric Cancer

(…) The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), doubleblind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease [see Clinical Studies (14.2)]. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. (…) 

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

(…) Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months) and region (Japan vs. US, Europe and Australia). The major effect outcome measure was overall survival (OS) and an additional effect outcome measure was progression-free survival (PFS). A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (52%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab. (See Table 7)

**12.5 Pharmacogenetics**

In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status.

**References**

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<td>G6PD</td>
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| 010670 | Tolbutamide | Endocrinology | G6PD | Precautions | Labeling not electronically available on Drugs@FDA |

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 (12.3)], 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 (PMs) 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 (12.3)]. 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)].

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Carbacic 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 18–55 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 QD, 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). (…) Tolerodine’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. (…)

12.3 Pharmacokinetics
Variability in Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6, the enzyme responsible for the formation of 5-HMT from tolterodine. The identified pathway of metabolism for these individuals (“poor metabolizers”) is via the cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as “extensive metabolizers.” Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HMT.
Excretion: Following administration of a 5 mg oral dose of 14C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (< 2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as 5-HMT.
A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine extended release and 5 HMT in extensive (EM) and poor (PM) metabolizers is provided in Table 3. These data were obtained following single and multiple doses of tolterodine extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM). (See Table 3) (…)

Drug Interactions:
Potent CYP2D6 inhibitors: Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate release in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine. Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be CYP2D6 extensive metabolizers of tolterodine immediate release to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate release and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered.

Potent CYP3A4 inhibitors: The effect of a 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were CYP2D6 poor metabolizers. In the presence of ketoconazole, the mean Cmax and AUC of tolterodine increased by 2- and 2.5 fold, respectively. Based on these findings, other potent CYP3A4 inhibitors may also lead to increases of tolterodine plasma concentrations. (…)
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| 020497, 05/12/2017                      | Toremifene | Oncology | ESR (Hormone Receptor) | Indications and Usage, Clinical Studies | **INICATIONS AND USAGE**
FARESTON® is an estrogen agonist/antagonist indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.

**14 CLINICAL STUDIES**
Three prospective, randomized, controlled clinical studies (North American, Eastern European, and Nordic) were conducted to evaluate the efficacy of FARESTON for the treatment of breast cancer in postmenopausal women. The patients were randomized to parallel groups receiving FARESTON 60 mg (FAR60) or tamoxifen 20 mg (TAM20) in the North American Study or tamoxifen 40 mg (TAM40) in the Eastern European and Nordic studies. The North American and Eastern European studies also included high-dose toremifene arms of 200 and 240 mg daily, respectively. The studies included postmenopausal patients with estrogen-receptor (ER) positive or estrogenreceptor (ER) unknown metastatic breast cancer. (…)

| 020281, 04/08/2019                      | Tramadol | Anesthesiology | CYP2D6 | Boxed Warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Patient Counseling Information | 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 tonsillectomy 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).

**5 WARNINGS AND PRECAUTIONS**

5.4 Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children
Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon post-marketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:
- ULTRAM is contraindicated for all children younger than 12 years of age (see Contraindications (4)).
- ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (see Contraindications (4)).
- Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose [see Use in Specific Populations (8.4), Overdosage (10)].

Nursing Mothers
Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultrarapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking ULTRAM could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with ULTRAM [see Use in Specific Populations (8.4)].

CYP2D6 Genetic Variability: Ultra-rapid metabolizers
Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)].

Individuals who are ultra-rapid metabolizers should not use ULTRAM.

8 USE IN SPECIFIC POPULATIONS

8.2 Lactation

Risk Summary
ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, O-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding [see Clinical Pharmacology (12)].

Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent.

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| 204114, 06/23/2020                      | Trametinib (1) | Oncology | BRAF | 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)]. (...)  
  
8.4 Pediatric Use  
The safety and effectiveness of ULTRAM in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol [see Warnings and Precautions (5.4)]. In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:  
• ULTRAM is contraindicated for all children younger than 12 years of age [see Contraindications (4)].  
• ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)].  
Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.  
  
12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Metabolism  
(…) Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower.  
(…) Poor / Extensive Metabolizers, CYP2D6  
The formation of the active metabolite, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower.  
  
17 PATIENT COUNSELING INFORMATION  
Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children  
Advise caregivers that ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 years of age receiving ULTRAM to monitor for signs of respiratory depression [see Warnings and Precautions (5.4)]. |}

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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 (14.4)]. 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) mg orally once daily or chemotheraphy (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, multi-cohort, 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 a nine-cohort, multicenter, non-randomized, 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
Administration of 1 mg and 2 mg MEKINIST to patients with BRAF V600E 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-positive, unresectable or metastatic melanoma. (…)
Tumor tissue was evaluated for BRAF mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients (96 patients treated with MEKINIST and 93 chemotherapy-treated patients) were also tested retrospectively using an FDA-approved companion diagnostic test, THxID™-BRAF assay. (…) The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (less than 1%). The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for patients treated with MEKINIST and 3.1 months for patients treated with chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST. (…)
MEKINIST with Dabrafenib
COMBI-d Study
The safety and efficacy of MEKINIST administered with dabrafenib were evaluated in an international, randomized, double-blind, active-controlled trial (the COMBI-d study; NCT01584648). The COMBI-d study compared dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment for patients with unresectable (Stage 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 M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing with the FDA-approved companion diagnostic test; 85% had BRAF V600E mutation-positive melanoma and 15% had BRAF V600K mutation-positive melanoma.
COMBI-MB Study
The activity of MEKINIST with dabrafenib for the treatment of BRAF V600E or V600K mutation-positive melanoma, metastatic to the brain, was evaluated in a non-randomized, open-label, multicenter, multi-cohort trial (the COMBI-MB study; NCT02039947). (…)
The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84 years), 58% were male, 100% were White, 8% were from the United States, 65% had a normal LDH value at baseline, and 97% had an ECOG performance status of 0 or 1.

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<td></td>
<td></td>
<td>Oncology</td>
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<tr>
<td>204114, 06/23/2020</td>
<td>Trametinib (2)</td>
<td>G6PD</td>
<td>Adverse Reactions</td>
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<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trials Experience</td>
<td>MEKINIST with Dabrafenib</td>
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<td>(…) The trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVOT or RPED, QTcB interval &gt;480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency. (…)</td>
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<td>204114, 06/23/2020</td>
<td>Trametinib (3)</td>
<td>RAS</td>
<td>Warnings and Precautions</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 New Primary Malignancies</td>
<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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<tr>
<td>103792, 11/29/2018</td>
<td>Trastuzumab (1)</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
<td></td>
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<td></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 negative or 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>as well as doxorubicin and cyclophosphamide, and either paclitaxel or docetaxel</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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<td>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.</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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<tr>
<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 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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 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.</td>
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<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
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<tr>
<td>12.2 Pharmacodynamics</td>
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<tr>
<td>Cardiac Electrophysiology</td>
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<td>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.</td>
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<tr>
<td>14 CLINICAL STUDIES</td>
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<td>14.1 Adjuvant Breast Cancer</td>
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<td>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) (…)</td>
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<td>14.2 Metastatic Breast Cancer</td>
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<td>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. (…)</td>
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<tr>
<td>14.3 Metastatic Gastric Cancer</td>
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<td>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, multicenter trial, 584 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and other variables (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2).</td>
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<th>Labeling Text</th>
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</table>
| 103792, 11/29/2018                     | Trastuzumab (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES  
Study 4  
(….) The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and chemotherapy therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2,197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1,868), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2,223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1,830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1,604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 3,448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.85). (See Table 9) (….) |
| 02/0438, 07/01/2008                    | Tretinoin | Oncology | PML-RARA | Indications and Usage, Warnings, Clinical Pharmacology | INDICATIONS AND USAGE  
VESANOID (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL). French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. VESANOID is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with VESANOID. |
| 213687, 06/30/2020                     | Triheptanoin | Inborn Errors of Metabolism | ACDVL, CPT2, HADHA, HADHB (Long-Chain Fatty Acid Oxidation Disorders) | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE  
DOJOLVI is indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD). |
| 016792, 07/17/2014                     | Trimipramine | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS  
Drugs Metabolized by P450 2D6  
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among African, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. (….) |
| 213411, 04/17/2020                     | Tucatinib | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
TUKYSA is indicated in combination with trastuzumab and capcitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. |

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<td>205382, 06/06/2019</td>
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<td>Pulmonary</td>
<td>CYP2D6</td>
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<td>211675, 08/16/2019</td>
<td>Upadacitinib</td>
<td>Rheumatology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
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<td>761044, 09/23/2016</td>
<td>Ustekinumab</td>
<td>Dermatology</td>
<td>IL12A, IL12B, IL23A</td>
<td>Warnings and Precautions</td>
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<td>209241, 08/10/2018</td>
<td>Valbenazine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Dosage and Administration</td>
<td></td>
</tr>
</tbody>
</table>

### 12 CLINICAL PHARMACOLOGY

#### 12.3 Pharmacokinetics

**Umeclidinium and Oxytremorine P450 2D6:**
In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (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).  

### 12 CLINICAL PHARMACOLOGY

#### 12.3 Pharmacokinetics

**Upadacitinib:**
Potential for Other Drugs to Influence the Pharmacokinetics of Upadacitinib
Upadacitinib is metabolized in vitro by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 3 (see Drug Interactions (7)).

### 12.3 Pharmacokinetics

**Ustekinumab:**
Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphoidal strains), and Bacillus Calmette-Guérin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

### 12.3 Pharmacokinetics

**Valbenazine:**
Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers (see Use in Specific Populations (8.6)).

### 12.2 Pharmacodynamic

**Cardiac Electrophysiology:**
(…) INGREZZA may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking an INGREZZA 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean QT prolongation of 11.7 msec (14.7 msec upper bound of double-sided 90% CI) as compared to otherwise healthy (ultrarapid, extensive, and intermediate metabolizers) and CYP2D6 poor metabolizer subjects (Figure 1).

### 12.1 HER2-Positive Metastatic Breast Cancer

The efficacy of TUKYSA in combination with trastuzumab and capectabine was evaluated in HER2CLIMB [see Clinical Studies (14)]. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capectabine or placebo plus trastuzumab and capectabine (n=404) or placebo plus trastuzumab and capectabine (n=197). The median duration of treatment was 7.5 months (range: 3 days, 2.9 years) for the TUKYSA arm. (…) 

### 14 CLINICAL STUDIES

#### 14.1 HER2-Positive Metastatic Breast Cancer

The efficacy of TUKYSA in combination with trastuzumab and capectabine was evaluated in 612 patients in HER2CLIMB (NCT02814794), a randomized (2:1), double-blind, placebo-controlled trial. Patients were required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases, and prior treatment with trastuzumab, pertuzuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. HER2 positivity was based on archival or fresh tissue tested with an FDA-approved test at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. (…)

### 5 WARNINGS AND PRECAUTIONS

#### 5.2 QT Prolongation

(…) INGREZZA may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking an INGREZZA 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean QT prolongation of 11.7 msec (14.7 msec upper bound of double-sided 90% CI) as compared to otherwise healthy volunteers given INGREZZA, who had a mean QT prolongation of 6.7 msec (8.4 msec) [see Warnings and Precautions (5.2)].

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<td>POLG</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
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<td>WARNING: LIFE THREATENING ADVERSE REACTIONS</td>
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<td>Patients with Mitochondrial Disease</td>
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<td>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 γ (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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<td>4 CONTRAINdications</td>
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<td>(…) Depakene is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders. 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 monitoring. The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug [see Boxed Warning and Contraindications (4)].</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Hepatotoxicity</td>
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<td>Patients with Known or Suspected Mitochondrial Disease</td>
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<td>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)]. Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders. 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 monitoring. The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug [see Boxed Warning and Contraindications (4)].</td>
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<td>5.6 Urea Cycle Disorders (UCD)</td>
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<td>Valproic acid is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders [see Contraindications (4) and Warnings and Precautions (5.10)].</td>
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<td>5.9 Hyperammonemia</td>
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<td>Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should also be considered in patients who present with hypothermia [see Warnings and Precautions (5.11)]. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders [see Contraindications (4) and Warnings and Precautions (5.6, 5.10)].</td>
</tr>
<tr>
<td>202429, 05/18/2020</td>
<td>Vemurafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration,</td>
<td>1 INDICATIONS AND USAGE</td>
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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>
</tr>
</tbody>
</table>

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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 (Trials 2 and 3). (See Table 6) In a single-arm, multinational trial (Trial 4), 132 patients with BRAF V600E mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, who had received dacarbazine 1000 mg/m² intravenously on Day 1 every 3 weeks (n=338). (See Table 5) Patients with BRAF V600E Mutation-Positive Metastatic Melanoma Who Received Prior Systemic Therapy (Trial 4). (See Table 4) ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.

1.2 Erdheim-Chester Disease

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation in tumor specimens prior to initiation of ZELBORAF [see Indications and Usage (1) and Dosage and Administration (2.1)].

5.2 Tumor Promotion in BRAF Wild-Type Melanoma

Concentration-dependent QT prolongation occurred in an uncontrolled, open-label QT sub-study in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [see Clinical Pharmacology (12.2)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of 960 mg twice daily. The median treatment duration for ECD patients in this study was 14.2 months. Table 3 presents adverse reactions reported in at least 20% of BRAF V600 mutation-positive ECD patients treated with ZELBORAF.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

This section describes adverse reactions identified from analyses of Trial 1 and Trial 2 [see Clinical Studies (14)]. (…) The most commonly reported adverse reactions (> 50%) in patients with BRAF V600E mutation-positive ECD treated with ZELBORAF were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The most common (≥ 10%) Grade 3 adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculo-papular, and arthralgia.

8.5 Pregnancy

This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 [see Clinical Studies (14)]. (…)

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

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., > 20 ms) from baseline. (…)

12.3 Pharmacokinetics

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.

14 CLINICAL STUDIES

Treatment-Naive Patients with BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma

Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naive, 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) Patients with BRAF V600E Mutation-Positive Metastatic Melanoma Who Received Prior Systemic Therapy (Trials 4). (See Table 4) ZELBORAF® is indicated 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) Patients with Wild-Type BRAF Melanoma

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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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<tbody>
<tr>
<td>202429, 05/18/2020</td>
<td>Venetoclax (1)</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Clinical Studies</td>
<td>ZELBORAF has not been studied in patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)]. Patients with Erdheim-Chester Disease (ECD) 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 V600 mutation–positive diseases. (…)</td>
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<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>ZELBORAF is indicated [see Dosage and Administration (2.1)]. (…)</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>17 PATIENT COUNSELING INFORMATION 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: • 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>
</tbody>
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<th>Labeling Text‡</th>
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</table>
| 208573, 05/29/2020                    | Venetoclax (2) | Oncology | Chromosome 11q | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy  
CCL14  
(…) Prior therapies included alkylation 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 unmethylated IgVH in 63%. (…)  
MURANO  
(…) Prior therapies included alkylation 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 unmethylated IgVH in 63%. (…) |
| 208573, 05/29/2020                    | Venetoclax (3) | Oncology | TP53 | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy  
CCL14  
(…) The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLO<70 mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmethylated IgVH in 57%. (…)  
MURANO  
(…) Prior therapies included alkylation 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 unmethylated IgVH in 63%. (See Table 17) (…) |
| 208573, 05/29/2020                    | Venetoclax (4) | Oncology | IDH1 | Clinical Studies | 14 CLINICAL STUDIES  
14.2 Acute Myeloid Leukemia  
Study M14-358  
VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02037733) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…)  
Study M14-387  
(…) 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. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months). The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes 25 cm, 30% of patients had ALC ≥2 x 10⁹/L, 33% had documented unmethylated IgVH, and 21% had documented 17p deletion. (…) |
| 208573, 05/29/2020                    | Venetoclax (5) | Oncology | IDH2 | Clinical Studies | 14 CLINICAL STUDIES  
14.2 Acute Myeloid Leukemia  
Study M14-358  
VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02037733) 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) (…) |

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<td>208573, 05/29/2020</td>
<td>Venetoclax (6)</td>
<td>Oncology</td>
<td>IGH</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy CCR 12 (…) The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had Clcr&lt;70mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmutated IgVH in 57%. (…) MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…) Study M12-175 (…) The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% of patients had ALC 255 x 109 /L, 33% had documented unmutated IgVH, and 21% had documented 17p deletion. (…) Study M14-382 (…) Of the 127 patients treated (91 with prior brutinib, 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 ≥5 x 109 /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 (7)</td>
<td>Oncology</td>
<td>NPM1</td>
<td>Clinical Studies</td>
<td>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 76 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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<td>Venetoclax (8)</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Clinical Studies</td>
<td>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 76 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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<td>04/02/2021, 211964</td>
<td>Viloxazine (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics CYP2D6 Metabolism A multiple-dose study was conducted with Quebree 900 mg once-daily in healthy volunteers to compare the effect of CYP2D6 poor metabolizers (PMs) and extensive metabolizers (EMs) on the PK of viloxazine. At steady state, viloxazine geometric means for Cmax and AUC0-24 were 21% and 26%, respectively, compared to EMs. (…)</td>
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<tr>
<td>04/02/2021, 211964</td>
<td>Viloxazine (2)</td>
<td>Psychiatry</td>
<td>SLC01B1</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics In Vitro Studies: Based on in vitro data, drugs that inhibit CYP enzymes 1A1, 1A2, 2B6, 2D6, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of viloxazine. Viloxazine does not inhibit CYP2C8, 2C9 or 2C19 activities. Viloxazine is a reversible inhibitor of P-gp, BCRP, MATE2-K, OATP1B1<em>1a, and OATP1B3 transporters. Viloxazine appears to be a weak inhibitor of the MATE1. Viloxazine is not a substrate of either OATP1B1</em>1a or OATP1B3 transporters.</td>
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<td>212154, 08/12/2020</td>
<td>Viltolarsen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE VILTEPSO 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 VILTEPSO [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.</td>
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<tr>
<td>202497, 06/08/2020</td>
<td>Vincristine</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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.</td>
</tr>
<tr>
<td>021266, 04/30/2019</td>
<td>Voriconazole</td>
<td>Infectious Diseases</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics The pharmacokinetics of voriconazole was evaluated in DMD patients following administration of intravenous (IV) doses ranging from 1.25 mg/kg/week (0.016 times the recommended dosage) to 80 mg/kg/week (the recommended dosage). Voriconazole exposure increased proportionally with dose, with minimal accumulation with once-weekly dosing. Inter-subject variability (as %CV) for Cmax and AUC ranged from 16% to 27% respectively. Voriconazole is administered as an IV infusion over 60 minutes. Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion). VILTEPSO is administered as an IV infusion over 60 minutes. Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion). Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion). Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion). Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion). Bioavailability is assumed to be 100%, and median Tmax was around 1 hour (end of infusion).</td>
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<tr>
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<tbody>
<tr>
<td></td>
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<td><strong>Labeling Text</strong></td>
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<tr>
<td></td>
<td><strong>NOA/ANDA/BLA</strong></td>
<td><strong>Drug</strong></td>
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<tr>
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<td><strong>Number, Label Version</strong></td>
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</tr>
<tr>
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<td><strong>Date</strong></td>
<td><strong>Biomarker‡</strong></td>
</tr>
<tr>
<td></td>
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<td><strong>Labeling Sections</strong></td>
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<tr>
<td>204447,</td>
<td>Warfarin (1)</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
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<tr>
<td>10/19/2018</td>
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<tr>
<td>213137,</td>
<td>Voxelotor</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
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<td>11/25/2019</td>
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<tr>
<td>009218,</td>
<td>Warfarin (1)</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
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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)].

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<tbody>
<tr>
<td>009218, 08/14/2017</td>
<td>Warfarin (2)</td>
<td>Hematology</td>
<td>VKORC1</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>CYP2C9 and VKORC1 Polymorphisms The S-enantiomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles, CYP2C9<em>2 and CYP2C9</em>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<em>2 and CYP2C9</em>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&gt;A) have been associated with variable warfarin dose requirements. VKORC1 and CYP2C9 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose of warfarin [see Dosage and Administration (2.3)].</td>
</tr>
<tr>
<td>009218, 08/14/2017</td>
<td>Warfarin (3)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
<td>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:</td>
</tr>
<tr>
<td>009218, 08/14/2017</td>
<td>Warfarin (4)</td>
<td>Hematology</td>
<td>PROC</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.8 Other Clinical Settings with Increased Risks In the following clinical settings, the risks of COUMADIN therapy may be increased:</td>
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doses overlap. This is consistent with the half-lives of the affected vitamin K-dependent clotting factors and anticoagulation proteins: Factor II - 60 hours, VII - 4 to 6 hours, IX - 24 hours, X - 48 to 72 hours, and proteins C and S are approximately 8 hours and 30 hours, respectively.