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 referenced drug as a perpetrator of an interaction with another drug; chromosomal abnormalities; selected proteins that are used for treatment selection are also included;

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;

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2020**

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<td>208716, 03/30/2020</td>
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</tbody>
</table>

<p>| Drug | Therapeutic Area* | Biomarker† | Labeling Sections | Labeling Text‡ |
|------|-------------------|------------|-------------------|----------------|----------------|
| 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 EndocrineBased Therapy Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician’s choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm. (…) MONARCH 2: VERZENIO in Combination with Fulvestrant Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy. The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2. (…) 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 study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. 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(…) | 1 INDICATIONS AND USAGE VERZENIO™ (abemaciclib) is indicated: • in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. • in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer 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 EndocrineBased Therapy Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. 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| 125427, 05/03/2019                      | Ado-Trastuzumab Emtansine | Oncology          | ERBB2 (HER2) | Indications, Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Metastatic Breast Cancer (MBC)  
KADCYLA®, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.  
Patients should have either:  
• Received prior therapy for metastatic disease, or  
• Developed disease recurrence during or within six months of completing adjuvant therapy.  
1.2 Early Breast Cancer (EBC)  
KADCYLA, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.  
Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA [see Dosage and Administration (2.1)]. |
| 05/03/2019                               | Emtansine          |                   |            |                   |               |
| 05/03/2019                               | Emtansine          |                   |            |                   |               |
| 05/03/2019                               | Emtansine          |                   |            |                   |               |
| 05/03/2019                               | Emtansine          |                   |            |                   |               |
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| Afatinib | Oncology     | EGFR       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | The adverse reactions described in Table 3 were identified in patients with HER2-positive metastatic breast cancer treated in the EMILIA trial [see Clinical Studies (14.1)]. Patients were randomized to receive KADCYLA or trastuzumab plus capcetibine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.6 months for patients treated with lapatinib and capcetibine, 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 three weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study. 12.3 Pharmacokinetics Effect of Hepatic Impairment The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment. (…) 14 CLINICAL STUDIES 14.1 Metastatic Breast Cancer The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial (EMILIA) (NCT00829166) of 991 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only prior adjuvant therapy were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. (…) 14.2 Early Breast Cancer KATHERINE (NCT01772472) was a randomized, multicenter, open-label trial of 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 chemotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory using Ventana’s PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluation after preoperative therapy. KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. (…) The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 84% of these patients received pertuzumab. (…) | 201292, 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 DOSEAGE AND ADMINISTRATION 2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC 2.1.1 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: http://www.fda.gov/CompanionDiagnoses. 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 | * 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. 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|--------|-------------------|------------|-------------------|------------------
| Alectinib | Oncology   | ALK        | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies | (...) The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naive, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 4 weeks 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 the remaining 11% had other mutations. Pre-specified exploratory subgroup analyses were conducted according to the stratification factor of EGFR mutation category. See Figure 2 and text below Figure 2.

Overall Response Rate In Other EGFR Mutations
The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions was evaluated in a pooled analysis of such patients enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148], LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT01121393]). • LUX-Lung 2 was a single arm, multicenter study of afatinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by the source document 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 2 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 days 8 and 21 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit. Among the 75 GILOTRIF treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. Among the 32 patients with a confirmed non-resistant EGFR mutation, the median age was 60.5 years (range 32-79), 60% were female, 97% were Asian, 3% were other races, 38% had an ECOG PS of 0, 63% had an ECOG PS 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIIb disease, and 88% had received 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.

1 INDICATIONS AND USAGE
ALECENSA is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of metastatic NSCLC with ALECENSA 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

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. Previously Untreated ALK-Positive Metastatic NSCLC
The safety of ALECENSA was evaluated in 152 patients with ALK-positive NSCLC in the ALEX study. The median duration of exposure to ALECENSA was 17.9 months. (…) ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib
The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with ALECENSA in two clinical trials, Studies NP28761 and NP28673. (…) 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects. In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration (Cmax,ss) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. (…) Absorption

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<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>Alectinib reached maximal concentrations at 4 hours following administration of ALECENSNA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC. (…) Distribution The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4. Alectinib and M4 are bound to human plasma proteins greater than 99.5%, independent of drug concentration. Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma. (…) Elimination The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC.</td>
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<tr>
<td>125241, 02/18/2020</td>
<td>Alglucosidase Alfa</td>
<td>Inborn Errors of Metabolism</td>
<td>GAA</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Immune-Mediated Reactions 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 clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. Immune tolerance induction administered prior to and in conjunction with initiation of alglucosidase alfa has been reported to aide tolerability of alglucosidase alfa in CRIM-negative patients. CRIM status has been shown to be associated with immunogenicity and patients' responses to enzyme replacement therapies. CRIM-negative infants with infantile-onset Pompe disease treated with alglucosidase alfa have shown poorer clinical response in the presence of high sustained IgG antibody titers and positive inhibitory antibodies compared to CRIM-positive infants [see Adverse Reactions (6.2)]. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained IgG antibody titers, including CRIM-negative patients (i.e., patients in whom no endogenous GAA protein was detected by Western blot analysis and/or predicted GAA activity was less than 5% of normal), may experience reduced clinical alglucosidase alfa treatment efficacy, such as loss of motor function, ventilator dependence, or death.</td>
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<tr>
<td>212526, 05/24/2019</td>
<td>Alpelisib (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.</td>
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<td>2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDAapproved tests for the detection of PIK3CA mutations in breast cancer 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 6.1 Clinical Trial Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)]. (…) 14 CLINICAL STUDIES SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2.</td>
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| 212526, 05/24/2019 | Alpelisib (2) | Oncology | ESR (Hormone Receptor) | Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 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. (…)

1 INDICATIONS AND USAGE
PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue.

Information on FDA approved tests for the detection of PIK3CA mutations in breast cancer is available at: http://www.fda.gov/CompanionDiagnostics.

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

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

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

212526, 05/24/2019 | Alpelisib (3) | Oncology | PIK3CA | Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 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. (…)

1 INDICATIONS AND USAGE
PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue.

Information on FDA approved tests for the detection of PIK3CA mutations in breast cancer is available at: http://www.fda.gov/CompanionDiagnostics.

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

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

There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. Of the 341 patients in the cohort with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the FDA-approved therascreen® PIK3CA RQ 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 RQ PCR Kit. Of the remaining 317 patients with PIK3CA mutations confirmed in tumor tissue, 177 patients (56%) had PIK3CA mutations identified in plasma specimen, and 140 patients (44%) did not have PIK3CA mutations identified in plasma specimen. (…) (…) Patient demographics for those with PIK3CA-mutated tumors were generally representative of the broader study population. The median duration of exposure to PIQRAY plus fulvestrant was 8.2 months with 56% of patients exposed for > 6 months. (…)

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| 209321, 05/06/2019                      | Amifampridine | Neurology | NAT2 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION

2.4 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers

The recommended starting dosage of RUZURGI in pediatric patients weighing 45 kg or more who are known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily taken orally in divided doses. The recommended starting dosage in pediatric patients weighing less than 45 kg who are known NAT2 poor metabolizers is 7.5 mg daily taken orally in divided doses [see Dosage and Administration (2.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.5)].

6 ADVERSE REACTIONS

(….) Subjects classified as poor metabolizers based on rate of metabolism were more likely to experience adverse reactions during RUZURGI treatment than intermediate or normal metabolizers [see Clinical Pharmacology (12.5)]. (…)

8 USE IN SPECIFIC POPULATIONS

8.8 NAT2 Poor Metabolizers

8 USE IN SPECIFIC POPULATIONS

8.8 NAT2 Poor Metabolizers

Exposure of RUZURGI is increased in patients who are N-acetyltransferase (NAT2) poor metabolizers [see Clinical Pharmacology (12.5)]. Therefore, initiate RUZURGI in patients who are known NAT2 poor metabolizers at the lowest recommended starting dosage and monitor for adverse reactions [see Dosage and Administration (2.5)]. Consider dosage modification of RUZURGI for patients who are known NAT2 poor metabolizers as needed based on clinical effect and tolerability.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of RUZURGI on QTc interval prolongation was studied in a double-blind, randomized, placebo- and positive-controlled study in 52 healthy volunteers (including 23 subjects with poor metabolizer phenotype). Study participants were administered 120 mg RUZURGI in 4 equal doses of 30 mg at 4-hour intervals (Dose 1, 2, 3, and 4)[see Clinical Pharmacology (12.5)]. RUZURGI did not prolong the QTc interval to any clinically relevant extent. In vitro, RUZURGI did not inhibit the human ether-à-go-go-related gene ion channel.

12.5 Pharmacogenomics

Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of RUZURGI metabolism. In normal healthy volunteers, poor metabolizers, also referred to as "slow acetylators" (i.e., carriers of two reduced function alleles) had higher average plasma amifampridine concentrations than intermediate metabolizers, also referred to as "intermediate acetylators" (i.e., carriers of one reduced and one normal function alleles), and normal metabolizers, also referred to as "fast/rapid acetylators" (i.e., carriers of two normal function alleles). In the TQT study [see Clinical Pharmacology (12.2)], poor metabolizers (N=19) had 6.0 to 8.5 times higher AUC0-4h and 6.1 to 7.6 times higher Cmax than intermediate metabolizers (N=3), following the first dose. Poor metabolizers had 6.0 to 8.5 times higher AUC0-4h and 6.1 to 7.6 times higher Cmax than normal metabolizers (N=3), following the first dose. 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).

| 208078, 11/28/2018 | Amifampridine Phosphate | Neurology | NAT2 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION

2.4 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers

The recommended starting dosage of FIRDAPSE in known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily, taken orally in 3 divided doses [see Use in Specific Populations (8.8) 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. The effect and tolerability.

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| 020541, 12/13/2018 | Anastrozole | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Adjuvant Treatment  
ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.  
1.2 First-Line Treatment  
ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer.  
1.3 Second-Line Treatment  
ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER negative disease and patients who did not respond to previous tamoxifen therapy were randomized to receive ARIMIDEX.  
6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
A post-marketing trial assessed the combined effects of ARIMIDEX and the bisphosphonate zoledronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture. (…)  
7 DRUG INTERACTIONS  
7.1 Tamoxifen  
Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial [see Clinical Studies (14.1)]. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole. (…) |
| 020541, 12/13/2018 | Amphetamine | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS  
Drugs Metabolized by P450 2D6  
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).  
In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. (…) |
| 072691, 07/17/2014 | Amitriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS  
Drugs Metabolized by P450 2D6  
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).  
In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. (…) |

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14 CLINICAL STUDIES
14.1 Adjuvant Treatment of Breast Cancer in Postmenopausal Women
At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. (…)
Patients in the two monotherapy arms of the ATAC trial were treated for a median of 60 months (5 years) and followed for a median of 68 months. Disease-free survival in the intent-to-treat population was statistically significantly improved [hazard ratio (HR) = 0.87, 95% CI: 0.78, 0.97, p = 0.0127] in the ARIMIDEX arm compared to the tamoxifen arm. In the hormone receptor-positive subpopulation representing about 84% of the trial patients, disease-free survival was also statistically significantly improved (HR = 0.83, 95% CI: 0.73, 0.94, p = 0.0049) in the ARIMIDEX arm compared to the tamoxifen arm. (See Figure 2) (…)
The frequency of individual events in the intent-to-treat population and the hormone receptor-positive subpopulation are described in Table 8. (See Tables 7 and 8)
A summary of the study efficacy results is provided in Table 9. (See Table 9, 10, and Figure 4) (…)
14.2 First-Line Therapy in Postmenopausal Women with Advanced Breast Cancer
Two double-blind, controlled clinical studies of similar design (0030, a North American study and 0027, a predominately European study) were conducted to assess the efficacy of ARIMIDEX compared with tamoxifen as first-line therapy for hormone receptor-positive or hormone receptor-negative locally advanced or metastatic breast cancer in postmenopausal women. (See Table 11) (…)
14.3 Second-Line Therapy in Postmenopausal Women with Advanced Breast Cancer who had Disease Progression following Tamoxifen Therapy
Anastrozole was studied in two controlled clinical trials (0004, a North American study; 0005, a predominately European study) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. Some of the patients had also received previous cytotoxic treatment. Most patients were ER-positive; a smaller fraction were ER-unknown or ER-negative; the ER-negative patients were eligible only if they had had a positive response to tamoxifen. (…)

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| 207533, 11/30/2018                     | Aripiprazole | Psychiatry | CYP2D6 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.4 Dose Adjustments for CYP450 Considerations
Refer to the prescribing information for oral aripiprazole for recommendations regarding dosage adjustments due to drug interactions, for the first 21 days when the patient is taking oral aripiprazole concomitantly with the first dose of ARISTADA.
Once stabilized on ARISTADA, refer to the dosing recommendations below for patients taking CYP 2D6 inhibitors, CYP 3A4 inhibitors, or CYP 3A4 inducers:
• No dosage changes recommended for ARISTADA, if CYP 450 modulators are added for less than 2 weeks.
• Make dose changes to ARISTADA if CYP 450 modulators are added for greater than 2 weeks. (See Table 4) |
| 021248, 06/20/2019                     | Arsenic Trioxide | Oncology | PML-RARA | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.1. Newly-Diagnosed Low-Risk APL
TRISENOX is indicated in combination with tretinoin for treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.
1.2. Relapsed or Refractory APL
TRISENOX is indicated for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. |
| 022466, 11/02/2018                     | Articaine and Epinephrine (1) | Anesthesiology | G6PD | Warnings and Precautions | 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 diaphasic 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. (…)

| 022466, 11/02/2018                     | Articaine and Epinephrine (2) | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions | 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 diaphasic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)

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| 761034, 05/29/2020                     | Atezolizumab (1) | Oncology | CD274 (PD-L1) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies | **1 INDICATIONS AND USAGE**

**1.1 Urothelial Carcinoma**

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

- are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test [see Dosage and Administration (2.1)]; or
- are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

**1.2 Non-Small Cell Lung Cancer**

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

**1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer**

TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test [see Dosage and Administration (2.1)].

This indication is approved under accelerated approval based on progression free survival [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection for Treatment of Urothelial Carcinoma and Triple-Negative Breast Cancer**

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

Select patients with first-line metastatic non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on the PD-L1 expression on tumor cells or on tumor infiltrating immune cells [see Clinical Studies (14.2)].

Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells [see Clinical Studies (14.3)].

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

Previously Treated Metastatic NSCLC

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

**6.2 Immuneoncology**

(….) 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**

**12.2 Pharmacokinetics**

Specific Populations

Age (21–89 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m2), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin ≤ 1.5 × ULN and AST < 1.5 × ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST), level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab. (….)

**14 CLINICAL STUDIES**

**14.1 Urothelial Carcinoma**

Cisplatin-Eligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

(….) Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 119 patients, 27% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area). The remaining 73% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumor infiltrating IC covering < 5% of the tumor area).

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 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.

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Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 14. 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 14) (…) Both cisplatin-eligible and cisplatin-eligible patients are included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of <5% when treated with TECENTRIQ monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended closure of the monotherapy arm to further accrual of patients with low PD-L1 expression, however, no other changes were recommended for the study, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

**Previously Treated Patients with Locally Advanced or Metastatic Urothelial Carcinoma**

(…) Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5%. The remaining 68% of patients were classified as having PD-L1 expression of < 5%.

**Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 15. 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: 31.3%, 34.7%). (See Table 15)** (…) **14.2 Non-Small Cell Lung Cancer**

**Metastatic Chemotherapy-Naive Non-Squamous NSCLC**

Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of IGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.

The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the IGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subgroup between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 16 and Figure 1. (…) The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with previously treated metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disorder, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppression within 2 weeks prior to enrollment were ineligible.

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; 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.

Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. non-squamous). Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. The major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PD-L1 expression on tumor cells [TC] or immune cells [IC]). In the subgroup of patients with PD-L1-expressing tumors, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

**14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer**

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<th>Biomarker†</th>
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<tr>
<td>761034, 05/29/2020</td>
<td>Atezolizumab (2)</td>
<td>Oncology</td>
<td>Gene Signature (T-effector)</td>
<td>Clinical Studies</td>
<td>*(…) Patients were stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) (PD-L1 stained tumor-infiltrating immune cells [IC] ≥ 1% of tumor area vs. &lt; 1% of tumor area) by the VENTANA PD-L1 (SP142) Assay. Of the 902 patients in the intent to treat population (ITT), 41% (369 patients) were classified as PD-L1 expression ≥ 1%. *(…) Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or an anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population. Tumor specimens (archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses. The major efficacy outcomes were investigator-assessed progression free survival (PFS) in the ITT and PD-L1 expressing patient population per RECIST v1.1 and overall survival (OS) in the ITT population. Overall survival data were immature with 43% deaths in the ITT population. The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 18 and Figure 3.</td>
</tr>
<tr>
<td>761034, 05/29/2020</td>
<td>Atezolizumab (3)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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 non-squamous 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 non-squamous 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.</td>
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<tr>
<td>761034, 05/29/2020</td>
<td>Atezolizumab (4)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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 non-squamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations.</td>
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</table>
| Atomoxetine | Psychiatry | CYP2D6 | Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION

2.4 Dosing in Specific Populations

Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs. In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

5 WARNINGS AND PRECAUTIONS

5.12 Laboratory Tests

Routine laboratory tests are not required. CYP2D6 metabolism. Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA (see Adverse Reactions section 1.1).

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); fatigue (6% of PMs, 1% of EMs); gastroenteritis (3% of PMs, 1% of EMs); syncope (3% of PMs, 1% of EMs); early morning awakening (2% of PMs, 1% of EMs); kyphosis (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 metabolizer (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metabolizer (EM) patients: vision blurred (4% of PMs, 1% of EMs); dry mouth (35% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs); feeling jittery (5% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); 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 Css, max is about 3- to 4-fold greater than atomoxetine alone.

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

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<td><strong>8 USE IN SPECIFIC POPULATIONS</strong></td>
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<tr>
<td><strong>8.1 Hepatic Insufficiency</strong></td>
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<td>Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency [see Dosage and Administration (2.3)].</td>
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<td><strong>8.7 Renal Insufficiency</strong></td>
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<td>EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.</td>
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<td><strong>8.9 Ethnic Origin</strong></td>
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<td>Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).</td>
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**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

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

**12.3 Pharmacokinetics**

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

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

Metabolism and elimination
Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and Css max is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. 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 equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, 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). (…)

**5 WARNINGS AND PRECAUTIONS**

**5.8 Glucose-6-phosphate dehydrogenase (G-6-PD) Deficiency**

Since MoviPrep contains sodium ascorbate and ascorbic acid, MoviPrep should be used with caution in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, especially G-6-PD deficiency patients with an active infection, with a history of hemolysis, or taking concomitant medications known to precipitate hemolytic reactions.
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| 212608, 01/09/2020                      | Avaparibib | Oncology | PDGFRA | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST) AVYAKIT 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 AVYAKIT 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 >5 cm, and 86% had prior surgical resection. The median number of prior kinase inhibitors was 1 (range: 0 to 5).
Efficacy results in patients with GIST harboring PDGFRA exon 18 mutations including the subgroup of patients with PDGFRA D842V mutations enrolled in NAVIGATOR are summarized in Table 5. (See Table 5)

5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

210238, 06/30/2019 | Avatrombopag (1) | Hematology | F2 (Prothrombin) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

210238, 06/30/2019 | Avatrombopag (2) | Hematology | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

210238, 06/30/2019 | Avatrombopag (3) | Hematology | PROC | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

210238, 06/30/2019 | Avatrombopag (4) | Hematology | PROS1 | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

210238, 06/30/2019 | Avatrombopag (5) | Hematology | SERPINC1 (Antithrombin III) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and

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| 016324, 12/20/2018 | Azathioprine (1) | Rheumatology     | TPMT       | Dosage and Administration, Warnings, 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, dosage reduction is recommended in patients known to have heterozygous deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests).

**WARNINGS**

Cytopenias

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06/30/2019 | Avatrombopag (6) | Hematology | CYP2C9 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

The CYP2C9*2 and CYP2C9*3 loss-of-function polymorphisms result in reduced CYP2C9 enzymatic activity. In a pooled pharmacogenomic analysis of avatrombopag studies, subjects heterozygous for CYP2C9 loss-of-function polymorphisms (intermediate metabolizers [n=24]) had approximately 1.4-fold higher exposure and subjects homozygous for CYP2C9 loss-of-function polymorphisms (poor metabolizers [n=2]) had approximately 2-fold higher exposure compared to subjects wild-type for CYP2C9 (normal metabolizers [n=94]).
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| 016324, 12/20/2018 | Azathioprine (2) | Rheumatology | NUDT15 | Dosage and Administration, Warnings, Precautions, Adverse Reactions, Clinical Pharmacology | DOSAGE AND ADMINISTRATION: Patients with TPMT and/or NUDT15 Deficiency

(…)

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

Heterozygous deficiency in TPMT and/or NUDT15

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

WARNINGS

Cytopenias

TPMT or NUDT15 Deficiency

(…)

Patients with thiopurine S-methyl transferase (TPMT) or nucleotide 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 reported in patients with absent TPMT activity receiving azathioprine. In patients with severe myelosuppression, consider evaluation for TPMT and NUDT15 deficiency (see PRECAUTIONS: Laboratory Tests). Consider alternative therapy in patients with homozygous TPMT or NUDT15 deficiency and reduced dosages in patients with heterozygous deficiency (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

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

ADVERSE REACTIONS

Hematologic

(…)

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

CLINICAL PHARMACOLOGY

(…)

6-MP undergoes two major inactivation routes. One is thiol methylation, which is catalyzed by the enzyme thiopurine Smethyltransferase (TPMT), to form the inactive metabolite methyl-6-MP (6-MeMP). Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) to form 6-thiouric acid. The nucleotide diphosphatase (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 TPMT or NUDT15 activity receiving usual doses of 6-MP or azathioprine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. Because of the risk of toxicity, patients with TPMT or NUDT15 deficiency require alternative therapy or dose modification (see DOSAGE AND ADMINISTRATION).

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 96% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Approximately 0.3% of patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. (…)

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Table of Pharmacogenomic Biomarkers in Drug Labeling

<table>
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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 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)].

12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the UGT1A1 gene and have little or no UGT1A1 activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function UGT1A1 allele leading to intermediate UGT1A1 activity (heterozygous deficient or intermediate metabolizers). The UGT1A1*28 allele accounts for about 95% of individuals with reduced levels of UGT1A1 activity. UGT1A1 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 UGT1A1 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of UGT1A1 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function UGT1A1 alleles have been observed. (…)

210498, 01/23/2019                     | Binimetinib (1) | Oncology | BRAF | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)].

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating MEKTOVI [Clinical Studies (14)]. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnosics.

5 WARNINGS AND PRECAUTIONS
5.3 Ocular Toxicities
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), 1 patient experienced RVO (0.1%). (…)

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

5.6 Rhabdomyolysis
Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevation of laboratory values of serum CPK occurred in 58% 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%). (…)

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<td>12.3 Pharmacokinetics</td>
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<td>Drug Interaction Studies</td>
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<td>Clinical Studies</td>
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<td>Effect of UGT1A1 Inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Simulations predict similar Cmax of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).</td>
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<td>12557, 03/20/2020</td>
<td>Binatumomab</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL</td>
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<td>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 = 207) or standard of care (SOC) chemotherapy (n = 199). (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 MRD-positive B-cell Precursor ALL</td>
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<td>BLAST Study</td>
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<td>The efficacy of BLINCYTO was evaluated in an open-label, multicenter, single-arm study (BLAST Study) [NCT01207388] that included patients who were ≥ 18 years of age, had received at least 3 chemotherapy blocks of standard ALL therapy, were in hematologic complete remission (defined as &lt; 5% blasts in bone marrow, absolute neutrophil count &gt; 1 G/L, platelets &gt; 100 G/L) and had MRD at a level of ≥ 0.1% using an assay with a minimum sensitivity of 0.01%. (See Table 11) (…)</td>
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<td>14.2 Relapsed/Refractory B-cell Precursor ALL</td>
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<td>Study MT103-211</td>
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<td>Study MT103-211 [NCT01466179] was an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL treated with BLINCYTO (n = 467) or standard of care (SOC) chemotherapy (n = 199). (…)</td>
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<td>ALCANTARA Study</td>
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<td>The efficacy of BLINCYTO for treatment of Philadelphia chromosome-positive B-cell precursor ALL was evaluated in an open-label, multicenter, single-arm study (ALCANTARA Study) [NCT02009427]. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-positive B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later tyrosine kinase inhibitor (TKI), or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate. (See Table 17) (…)</td>
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<tr>
<td>202258, 01/30/2017</td>
<td>Boceprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to PegIntron/REBETOL. IL28B rs12979860 was genotyped in 653 of 1048 (62%) subjects in SPINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPOND-2 (previous partial responders and relapsers) [see Clinical Studies (14) for trial descriptions]. Among subjects that received at least one dose of placebo or VICTRELIS (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 VICTRELIS. The results of this retrospective subgroup analysis should be viewed</td>
</tr>
</tbody>
</table>

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<td>203341, 10/09/2019</td>
<td>Bosutinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>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>

### 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.

**Newly-Diagnosed CP Ph+ CML**

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

**CP, AP, or BP Ph+ CML with Resistance or Intolerance to Prior Therapy**

The recommended dose and schedule of BOSULIF is 500 mg orally once daily with food.

#### 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, antidiarrheals, 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 Grade 4 cardiac 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 I/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 chrOnc 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 >5 (modified intent-to-treat [mITT] population). Randomization was stratified by Sokal score and geographical region. All patients

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| 125388, 10/15/2019                      | Brentuximab Vedotin (1) | Oncology   | ALK        | Clinical Studies  | 14.2 Systemic Anaplastic Large Cell Lymphoma (…)
|                                        |      |                   |            |                   |                |
| 125388, 10/15/2019                      | Brentuximab Vedotin (2) | Oncology   | TNFRSF8 (CD30) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 14.4 Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides (…)

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<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
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<td>2 DOSEAGE AND ADMINISTRATION</td>
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<td>2.9 Dose Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inhibitors or Inducers</td>
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<td>Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). If the coadministered drug is discontinued, adjust the REXULTI dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks [see Drug Interactions (7.1), Clinical Pharmacology (12.3)]. (See Table 1)</td>
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<td>ALK</td>
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<td>1 INDICATIONS AND USAGE</td>
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<td>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>
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<td>12.3 Pharmacokinetics</td>
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<td>Drug Interaction Studies</td>
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<td>Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors [see Drug Interactions (7.1)].</td>
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<td>018644, 11/05/2019</td>
<td>Bupropion</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Brivacacetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxyl metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidas. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variants in CYP2C19, production of the hydroxyl metabolite is decreased 2-fold or 10-fold, while the blood level of brivacacetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.</td>
</tr>
<tr>
<td>009366, 12/24/2003</td>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>(…) Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph) chromosome. Also, the so-called “juvenile” type of chronic myelogenous leukemia, typically occurring in young children and associated with the absence of a Philadelphia chromosome, responds poorly to busulfan. The drug is of no benefit in patients whose chronic myelogenous leukemia has entered a “blastic” phase. (…)</td>
</tr>
<tr>
<td>203756, 01/31/2020</td>
<td>Cabozantinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Clinical Studies</td>
<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>020896, 02/22/2019</td>
<td>Capecitabine</td>
<td>Oncology</td>
<td>DPDYD</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<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</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Date</th>
<th>Number, Label Version</th>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/20/2018</td>
<td>016608, (2)</td>
<td>Carbamazepine</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>BOXED WARNING</td>
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<tr>
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<td></td>
<td></td>
<td>Serious dermatologic reactions and HLA-B*1502 allele</td>
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<td>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*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>
<tr>
<td>03/20/2018</td>
<td>016608, (1)</td>
<td>Carbamazepine</td>
<td>Neurology</td>
<td>HLA-A</td>
<td>Warnings</td>
<td>WARNINGS</td>
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<td></td>
<td>Serious Dermatologic Reactions</td>
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<th>Biomarker‡</th>
<th>Labeling Sections</th>
<th>Labeling Text†</th>
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<tr>
<td>022562, 12/23/2019</td>
<td>Carisoprodol</td>
<td>Rheumatology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATION 8.8 Patients with Reduced CYP2C19 Activity</td>
</tr>
<tr>
<td>022562, 12/23/2019</td>
<td>Cariprazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics CYP2D6 Poor Metabolizers CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR. Drug Interaction Studies CYP2D6 inhibitors CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.</td>
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<tr>
<td>011792, 05/24/2019</td>
<td>Carisoprodol</td>
<td>Rheumatology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATION 8.8 Patients with Reduced CYP2C19 Activity</td>
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<td>Clinical Pharmacology</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</td>
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<td>The major pathway of carisoprodol metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism (see Patients with Reduced CYP2C19 Activity below).</td>
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<td>Patients with Reduced CYP2C19 Activity</td>
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<td>SOMA should be used with caution in patients with reduced CYP2C19 activity.</td>
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<td>Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carisoprodol, and concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.</td>
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<td>7 DRUG INTERACTIONS</td>
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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>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared with extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-methylenedioxyphenethylamine (patients deficient in cytochrome P450 2C19).</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>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>
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<td>8.8 Poor Metabolizers of CYP2C9 Substrates</td>
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<td>In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*1/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer CELEBREX starting with half the lowest recommended dose.</td>
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<td>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>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9<em>2 and CYP2C9</em>3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/<em>3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9</em>1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6) and Use in Specific Populations (8.8)].</td>
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<td>12.3 Pharmacokinetics</td>
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<td>carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared with extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-methylenedioxyphenethylamine (patients deficient in cytochrome P450 2C19).</td>
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</table>
| 205755, 03/05/2019                     | Ceritinib | Oncology | ALK        | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 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. |
|                                        |       |                  |            |                  |               |
| 761052, 12/06/2019                     | Cerliponase Alfa | Inborn Errors of Metabolism | TPP1       | Indications and Usage, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
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 peptidase 1 (TPP1) deficiency. |

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<td>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>
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<td><strong>14 CLINICAL STUDIES</strong></td>
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<td>The efficacy of Brineura was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency. (…) Motor scores of the 22 Brineura-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study. The results of logistic modeling with covariates (screening age, screening motor score, genotype: 0 key mutations (yes/no)), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% CI): 13.1 (1.2, 146.9)). (…) Descriptive non-randomized comparison (…) Given the non-randomized study design, a Cox Proportional Hazards Model adjusted for age, initial motor score, and genotype was used to evaluate time to unreversed 2-category decline or unreversed score of 0 in the Motor domain. This model showed a lesser decrease in motor function in the Brineura-treated patients when compared to the natural history cohort (see Figure 7). (…) Motor Domain Scores: Matched Patients Only (…) To further assess efficacy, the 22 patients from the Brineura clinical study with a baseline combined Motor plus Language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. Patients were matched based on the following covariates: baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening. (see Table 3) (…)</td>
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<tr>
<td>125084, 04/23/2019</td>
<td>Cetuximab (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</td>
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<tr>
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<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 Pharmacology (12.1), 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 the results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)].</td>
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<td><strong>2 DOSAGE AND ADMINISTRATION</strong></td>
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<td>2.2 Colorectal Cancer</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 colorectal cancer is available at: <a href="http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm">http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm</a></td>
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<td><strong>6 ADVERSE REACTIONS</strong></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 (…) The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…) As Monotherapy (…) The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)]. ERBITUX was administered intravenously at the recommended dosage (400 mg/m2 initial dose, followed by 250 mg/m2 weekly). Patients received a median of 17 infusions (range 1 to 51) [see Clinical Studies (14.2)]. (See Table 5) (…) In Combination with Irinotecan ERBITUX at the recommended dosage was administered in combination with irinotecan in 354 patients with EGFR expressing recurrent mCRC in Study CP02-9923 and BOND. (…)</td>
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<td><strong>14 CLINICAL STUDIES</strong></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 CRYSTAL (NCT001540102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive either a cetuximab product in combination with FOLFIRI or FOLFIRI alone as first-line treatment. Stratification factors were Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 versus 2) and region (Western Europe versus Eastern Europe versus other). (…) As Monotherapy Study CA225-025 (NCT00079066) was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent mCRC. (See Table 9) (…) In Combination with Irinotecan</td>
</tr>
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<th>Biomarker‡</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</thead>
</table>
| 125084, 04/23/2019 | Cetuximab (2) | Oncology | RAS | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE

### 1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer

Erbitux is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use (see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Studies (14.2)):  
- in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment,  
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,  
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. [See Warnings and Precautions (5.7), Clinical Pharmacology (12.1), Clinical Studies (14.2).]

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.2 Colorectal Cancer

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

### 5 WARNINGS AND PRECAUTIONS

#### 5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC

Erbitux is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as “Ras” or when the Ras status is unknown. Retrospective subset analyses of RAS-mutant and wild-type populations across several randomized clinical trials including Study 4 were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. [See Indications and Usage (1.2), Clinical Pharmacology (12.1), Clinical Studies (14.2).]

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

**K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)**

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 687 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…)

As Monotherapy

The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA22S-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) (…)

### 14 CLINICAL STUDIES

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

In Combination with FOLFIRI

(…) K-Ras mutation status was available for 89% of the patients: 63% had K-Ras wild-type tumors and 37% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. Baseline characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population. (…)

(…) Results of the planned PFS and ORR analysis in all randomized patients and post-hoc 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, and post-hoc analysis of updated OS based on additional followup (1000 events) in all randomized patients and in subgroups of patients defined by K-Ras mutation status are presented in Table 8 and Figure 2. The treatment effect in the all-randomized population for PFS was driven by treatment effects limited to patients who have K-Ras wild-type tumors. There is no evidence of effectiveness in the subgroup of patients with K-Ras mutant tumors. (See Table 8 and Figure 2) (…)

(…) K-Ras status was available for 79% of the patients: 54% had K-Ras wild-type tumors and 46% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. (See Table 9 and Figure 3) (…)

In Combination with Irinotecan

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

### 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, 3A4 were not inhibited by exposure to cevimeline. (…)

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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 Hematological Effects/Laboratory Tests Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered. The drug should be administered with caution to patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.</td>
</tr>
<tr>
<td>011641, 02/01/2011</td>
<td>Chloroprocaine</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Hemolytic Anemia Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because DIABINESE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.</td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>018057, 02/22/2019</td>
<td>Cisplatin</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS Ototoxicity (+) Genetic factors (e.g., variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.</td>
</tr>
<tr>
<td>020822, 01/11/2019</td>
<td>Citalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Dosage and Administration</td>
<td>DOSAGE AND ADMINISTRATION Special Populations 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>
</tr>
<tr>
<td>020822, 01/11/2019</td>
<td>Citalopram (2)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY Pharmacokinetics Population Subgroups (+) CYP2C19 poor metabolizers – In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celsena 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION). CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.</td>
</tr>
<tr>
<td>202067, 06/15/2018</td>
<td>Clobazam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Dosage and Administration</td>
<td>2 DOSAGE AND ADMINISTRATION 2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam’s active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1.</td>
</tr>
</tbody>
</table>

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<tr>
<td>019906, 05/10/2019</td>
<td>Clomipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td></td>
<td>Drugs Metabolized by P450 2D6</td>
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</table>
|                                        |              |                   |            |                   | 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). (…)

| 020839, 05/17/2019                     | Clopidogrel  | Cardiology        | CYP2C19    | Boxed Warning, Warnings and Precautions, Clinical Pharmacology | BOXED WARNING |
|                                        |              |                   |            |                   | Diminished antplatelet effect in patients with two loss-of-function alleles of the CYP2C19 gene |
|                                        |              |                   |            |                   | The effectiveness of Plavix results from its conversion to an active metabolite by the cytochrome P450 (CYP) 2C19 system, principally CYP2C19 (see Warnings and Precautions (6.1), Clinical Pharmacology (12.3)). Plavix recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.3)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. |

| 019758, 02/23/2017                     | Clozapine    | Psychiatry        | CYP2D6     | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION |
|                                        |              |                   |            |                   | 2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers |
|                                        |              |                   |            |                   | It may be necessary to reduce the CLOZARIL dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)]. |

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<tbody>
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<td>Codeine</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<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.</td>
</tr>
<tr>
<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: COTELLIC® is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.</td>
</tr>
</tbody>
</table>

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<td>761128, 11/15/2019</td>
<td>Crizanlizumab-tmca</td>
<td>Hematology</td>
<td>HBB</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trials Experience</td>
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<tr>
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<td></td>
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<td>Sickle Cell Disease</td>
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</tbody>
</table>
|                                        |                               |                   |            |                   | 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, Hb S beta0-thalassemia, Hb S beta+ -thalassemia, and others). (…)

14 CLINICAL STUDIES
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, Hb S beta0-thalassemia, Hb S beta+ -thalassemia, and others), and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. (See Table 2) (…). (…)

(…)

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…)

The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 106 patients who crossed over from the control arm), 2, 3, a single arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154). The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3). (…)

Previously Untreated ALK-Positive Metastatic NSCLC – Study 1 (PROFILE 1014)
The data in Table 3 are derived from 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). (…)

ROSI-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=96). Vision disorders occurred in 92% of patients in Study 3; 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months.

202570, 06/25/2019
Crizotinib (1)
Oncology
ALK
1 INDICATIONS AND USAGE
XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)].

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…)

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…)

The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 106 patients who crossed over from the control arm), 2, 3, a single arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154). The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3). (…)

Previously Untreated ALK-Positive Metastatic NSCLC – Study 1 (PROFILE 1014)
The data in Table 3 are derived from 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). (…)

ROSI-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=96). Vision disorders occurred in 92% of patients in Study 3; 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months.

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</table>
| 202570, 06/25/2019                     | Crizotinib (2) | Oncology | ROS1 | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)].

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…)

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use
Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

14 CLINICAL STUDIES
14.1 ALK-Positive Metastatic NSCLC
Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014; NCT01154140)
The efficacy and safety of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 1). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit, prior to randomization. (See Table 7) (…)

Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007; NCT00932893)
The efficacy and safety of XALKORI as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum based chemotherapy regimen, were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). (…) Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization. A total of 112 (64%) patients randomized to the chemotherapy arm subsequently received XALKORI after disease progression. (See Table 8) (…)

14.2 ROS1-Positive Metastatic NSCLC
ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001; NCT00585195)
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 90% of patients in Study 3, 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months.

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<td>202806, 04/09/2020</td>
<td>Dabrafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
<td>The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older, ECOG performance status of 0, 1, or 2, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRR and investigator, with imaging performed every 8 weeks for the first 60 weeks. Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (80%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required a ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. (See Table 9)</td>
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<td>TAFINLAR as a Single Agent</td>
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<td>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 310 mg).</td>
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<td><strong>Malignant Melanoma</strong></td>
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<td><strong>Metastatic or Unresectable BRAF V600 Mutation Positive Melanoma</strong></td>
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<tr>
<td>TAFINLAR Administered with Trametinib</td>
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<td>The safety of TAFINLAR when administered with trametinib was evaluated in 509 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.</td>
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<td><strong>Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma</strong></td>
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<td>The safety of TAFINLAR when administered with trametinib was evaluated in 31 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)].</td>
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<td>TAFINLAR Administered with Trametinib</td>
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<td>The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928).</td>
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<td><strong>Locally Advanced or Metastatic BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC)</strong></td>
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<td>The safety of TAFINLAR when administered with trametinib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019).</td>
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<td><strong>BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent</strong></td>
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<td><strong>BREAK-3</strong></td>
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<td>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.</td>
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<td>(…) 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.</td>
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<td>(…) In supportive analyses based on IRRC assessment and in an exploratory subgroup analysis of patients with confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis.</td>
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<td><strong>BREAK4M</strong></td>
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<td>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-4M study; NCT01266967).</td>
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<td><strong>12.2 Pharmacodynamics</strong></td>
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<td>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., &gt;20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage).</td>
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<td><strong>14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR Administered with Trametinib</strong></td>
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<td><strong>COMBI-d Study and COMBI-v Study</strong></td>
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<td>The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01586468) and one open-label trial (the COMBI-v study; NCT01597088).</td>
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<td>The COMBI-d study compared TAFINLAR and trametinib as placebo-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 (&gt;= the upper limit of normal ULN) vs. &lt; 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).</td>
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<td>The COMBI-v study compared TAFINLAR and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (&gt;= the upper limit of normal ULN) vs. &lt; ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was overall survival. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1. (…)</td>
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<td>(…) 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. (…)</td>
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<td>In the COMBI-v study, 704 patients were randomized to TAFINLAR plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91 years), 96% were White, and 55% were male. 6% percent of patients had Stage IIC, 61% had M1c disease, 67% had a normal LDH.</td>
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<td>Dabrafenib (2)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions, Patient Counseling Information</td>
<td>70% had ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases. (See Table 12 and Figures 2, 3) COMBI-MB Study (...) The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84 years), 58% were male, 100% were white, 8% were from the United States, 65% had a normal LDH value at baseline, and 97% had an ECOG performance status of 0 or 1. Intracranial metastases were asymptomatic in 87% and symptomatic in 13% of patients, 22% received prior local therapy for brain metastases, and 87% also had extracranial metastases. (...) 14.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma COMBI-AD (NCT 01692083) 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 Tyro3™-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 or V600K) and American Joint Committee on Cancer (AJCC, 7th Edition) stage (Ila, Iib, or IIIa). (...) In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range 18-89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage Ila (18%), Stage IIb (41%), Stage IIIa (40%), stage unknown (1%); BRAF V600E mutation (91%); BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 14) (...) 14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC) In Study BRF119328 (NCT01336364), 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 BRF117019 (NCT02034110), an activity estimating, nine-cohort, multi-center, non-randomized, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication, who received prior treatment with BRAF or MEK inhibitors; with symptomatic or untreated CNS metastases; or who had airway obstruction. (...) 17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients of the following: Confirmation of BRAF V600 mutation • TAFINLAR as a single agent: Evidence of BRAF V600E mutation in the tumor specimen using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)]. • TAFINLAR with trametinib: Evidence of BRAF V600E mutation in tumor specimens using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)]. (...) 5 WARNINGS AND PRECAUTIONS 5.9 Glucose-6-Phosphate Dehydrogenase Deficiency TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Metastatic or Unresectable BRAF V600E or V600K Mutation-Positive Melanoma TAFINLAR as a Single Agent Table 3 and Table 4 present adverse drug reactions identified from analyses of the BREAK-3 study [see Clinical Studies (14.1)]. This study, a multicenter, international, open-label, randomized (3:1), controlled trial enrolled 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). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥ Grade 2), corrected QT interval greater than or equal to 480 milliseconds on electrocardiogram, or a known history of glucose-6-phosphate dehydrogenase deficiency. (...) 17 PATIENT COUNSELING INFORMATION Glucose-6-phosphate dehydrogenase (G6PD) deficiency TAFINLAR may cause hemolytic anemia in patients with G6PD deficiency. Advise patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis [see Warnings and Precautions (5.9)].</td>
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| 202808, 04/09/2020 | Dabrafenib (3) | Oncology | RAS | Dosage and Administration, Warnings and Precautions | 2 DOSAGE AND ADMINISTRATION  
2.3 Dosage Modifications for Adverse Reactions  
Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies. (See Table 2)  
5 WARNINGS AND PRECAUTIONS  
5.1 New Primary Malignancies  
Non-cutaneous Malignancies  
Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Across clinical trials of TAFINLAR monotherapy and TAFINLAR administered with trametinib, non-cutaneous malignancies occurred in 1% of patients. Monitor patients receiving TAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies [see Dosage and Administration (2.7)]. |
| 206843, 11/09/2017 | Daclatasvir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14 CLINICAL STUDIES  
14.2 Clinical Trials in HCV Genotype 3 (ALLY-3)  
(…) The 152 treated subjects in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the subjects were male; 90% were white, 5% were Asian, and 4% were black. Most subjects (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype. SVR12 and outcomes in subjects without SVR12 in ALLY-3 are shown by patient population in Table 13. SVR12 rates were comparable regardless of 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). (…)  
14.3 Clinical Trials in HCV/HIV Coinfected Subjects (ALLY-2)  
(…) Most subjects (80%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 16% of the subjects had compensated cirrhosis, and 73% had IL28B rs12979860 non-CC genotype. (…)  
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). (…)  
14.4 Clinical Trials in Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Recurrence after Liver Transplantation (ALLY-1)  
(…) Fifty-eight percent of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6. 77% had IL28B rs12979860 non-CC genotype. (…)  
SVR12 rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level. For SVR12 outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…) |
| 211288, 09/27/2018 | Dacomitinib | Oncology | EGFR | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE  
VIZIMPRO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test [see Dosage and Administration (2.1)].  
2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
Select patients for the first-line treatment of metastatic NSCLC with VIZIMPRO based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.  
6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
(…) The data in the Warnings and Precautions section reflect exposure to VIZIMPRO in 394 patients with first-line or previously treated NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations who received VIZIMPRO at the recommended dose of 45 mg once daily in 4 randomized, active-controlled trials [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), and Study A7471028 (N=16)] and one single-arm trial [Study A7471017 (N=30)]. The median duration of exposure to VIZIMPRO was 10.8 months (range 0.07-68) [see Warnings and Precautions (5)].  
The data described below reflect exposure to VIZIMPRO in 227 patients with EGFR mutation-positive, metastatic NSCLC enrolled in a randomized, active-controlled trial [ARCHER 1050]; 224 patients received gefitinib 250 mg orally once daily in the active control arm [see Clinical Studies (14)].  
8 USE IN SPECIFIC POPULATIONS  
8.5 Gender Use  
Of the total number of patients (N=394) in five clinical studies with EGFR mutation-positive NSCLC who received VIZIMPRO at a dose of 45 mg orally once daily [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), Study A7471028 (N=16), and Study A7471017 (N=30)] 40% were 65 years of age and older. (…)  
14 CLINICAL STUDIES  
The efficacy of VIZIMPRO was demonstrated in a randomized, multicenter, multinational, open-label study [ARCHER 1050; [NCT01774721]]. Patients were required to have unresectable, metastatic NSCLC with no prior therapy for metastatic disease or recurrent disease with a minimum of 12 months disease-free after completion of systemic therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.  
Select patients for the first-line treatment of metastatic NSCLC with VIZIMPRO based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.  
Select patients for the first-line treatment of metastatic NSCLC with VIZIMPRO based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.  
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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
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<td>021794, 05/18/2018</td>
<td>Dapsone (1)</td>
<td>Dermatology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>Dapsone (1) Pharmacogenomic Biomarker. EGFR mutation status was prospectively determined by local laboratory or commercially available tests (e.g., therascreen® EGFR RGQ PCR and cobas® EGFR Mutation Test). Patients were randomized to receive VIZIMPRO 45 mg orally once daily or gefitinib 250 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by region (Japanese versus mainland Chinese versus other East Asian versus non-East Asian), and EGFR mutation status (exon 19 deletions versus exon 21 L858R substitution mutation). (...) Prognostic and tumor characteristics were ECOG performance status 0 (30%) or 1 (70%); 69% with exon 19 deletion and 41% with exon 21 L858R substitution; Stage IIIB (8%) and Stage IV (92%); 64% were never smokers; and 1% received prior adjuvant or neoadjuvant therapy. (…)</td>
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| 021794, 05/18/2018                    | Dapsone (2) | Dermatology | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions, Adverse Reactions, Patient Counseling Information | Dapsone (2) Pharmacogenomic Biomarker. Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE® Gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of ACZONE® Gel, 5% in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of ACZONE® Gel, 5%, with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency. |

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<td>066841</td>
<td>Dapsone (3)</td>
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<td>G6PD</td>
<td>Precautions, Adverse Reactions, Overdosage</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<td>021513, 03/15/2012</td>
<td>Darifenacin</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics</td>
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<td>Electrolyteology</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 (moloxifloxin 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 moloxifloxin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the clinical efficacy and safety studies, the change in median HR following treatment with Enablex was no different from placebo.</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Absorption</td>
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<td>After oral administration of Enablex to healthy volunteers, peak plasma concentrations of darifenacin are reached approximately seven hours after multiple dosing and steady-state plasma concentrations are achieved by the sixth day of dosing. The mean (SD) steady-state time course of Enablex 7.5 mg and 15 mg extended-release tablets is depicted in Figure 1. A summary of mean (standard deviation, SD) steady-state pharmacokinetic parameters of Enablex 7.5 mg and 15 mg extended-release tablets in EMs and PMs of CYP2D6 is provided in Table 3. The mean oral bioavailability of Enablex in EMs at steady-state is estimated to be 15 percent and 19 percent for 7.5 mg and 15 mg tablets, respectively. (See Figure 1 and Table 3)</td>
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<td>Variability in Metabolism</td>
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<td>A subset of individuals (approximately 7 percent Caucasians and 2 percent African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs.</td>
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<td>Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM versus EM) for Cmax and AUC following darifenacin 15 mg once daily at steady-state were 1.9 and 1.7, respectively.</td>
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<td>Excretion</td>
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<td>Following administration of an oral dose of 14C-darifenacin solution to healthy volunteers, approximately 60 percent of the radioactivity was recovered in the urine and 40 percent in the feces. Only a small percentage of the excreted dose was unchanged darifenacin (3 percent). Estimated darifenacin clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life of darifenacin following chronic dosing is approximately 13 to 19 hours.</td>
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<td>Drug-Drug Interactions</td>
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<td>CYP3A4 inhibitors</td>
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<td>In a drug interaction study, when a 7.5 mg once daily dose of Enablex was given to steady-state co-administered with the potent CYP3A4 inhibitor ketoconazole 400 mg, mean darifenacin Cmax increased to 11.2 ng/mL for EMs (n = 10) and 59.4 ng/mL for one PM subject (n = 1). Mean AUC increased to 143 and 939 ng•h/mL for EMs and for one PM subject, respectively. When a 15 mg daily dose of Enablex was given with ketoconazole, mean darifenacin Cmax increased to 67.6 ng/mL and 58.9 ng/mL for EMs (n = 3) and one PM subject (n = 1), respectively. Mean AUC increased to 1110 and 931 ng•h/mL for EMs and for one PM subject, respectively (see Dosage and Administration (2) and Drug Interactions (7.1)).</td>
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<td>206619, 07/23/2018</td>
<td>Dasabuvir, Ombitasvir, Paritaprevir, and Rivaroxaban</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis</td>
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<td>Subjects with Chronic HCV GT1a Infection without Cirrhosis</td>
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<td>Subjects with HCV GT1a infection without cirrhosis treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV [see Clinical Studies (14.1)] had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 19% had a body mass index of at least 30 kg per m²; 55% of patients were enrolled in US sites; 72% had IL28B (rs12979860) non-CC genotype; 85% had baseline HCV RNA levels of at least 800,000 IU per mL, (…), Subjects with Chronic HCV GT1b Infection without Cirrhosis</td>
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<td>Subjects with HCV GT1b infection without cirrhosis were treated with VIEKIRA PAK with or without RBV for 12 weeks in PEARL-II and -III [see Clinical Studies (14.1)]. Subjects had a median age of 52 years (range: 18 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were</td>
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</table>
| 021986, 12/21/2018                      | Dasatinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | Hispanic or Latino; 21% had a body mass index of at least 30 kg per m². 21% of patients were enrolled in US sites; 83% had IL28B (rs12979860) nonCC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per mL. (…)

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 58 years (range: 21 to 71); 70% of the subjects were male; 95% were White; 3% were Black/African American; 12% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m²; 43% of patients were enrolled in US sites; 82% had IL28B (rs12979860) non-CC genotype; 86% had baseline HCV RNA levels of at least 800,000 IU per mL; 69% had HCV GT1a infection; 42% were treatment-naive, 36% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders; 14% were prior pegIFN/RBV relapsers; 15% had platelet counts of less than 90 x 10⁹ per L; 50% had albumin less than 4.0 mg per dL; (…) (…) TURQUOISE-III was an open-label trial that enrolled 60 HCV GT1b-infected subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naive or did not achieve SVR with prior treatment with pegIFN/RBV. Subjects received VIEKIRA PAK without RBV for 12 weeks. Treated subjects had a median age of 61 years (range: 26 to 78); including 40% treatment-naive and 50% pegIFN/RBV treatment-experienced; 25% were ≥65 years; 62% were male; 12% were Black; 5% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m²; 40% of patients were enrolled in US sites; 22% had platelet counts of less than 90 x 10⁹ per L; 17% had albumin less than 35 g/L; 92% had baseline HCV RNA levels of at least 800,000 IU per mL; 83% had IL28B (rs12979860) non-CC genotype; (…)

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

(…) Treated subjects had a median age of 51 years (range: 31 to 69); 24% of subjects were black; 81% of subjects had IL28B (rs12979860) non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naive; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection; (…)

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.

2 DOSAGE AND ADMINISTRATION

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 for Ph+ 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 with 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+ AML) in patients who tolerate the starting dose. 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 resume at 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 adults and in pediatric patients with chronic phase CML was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response [CCyR] or major molecular response [MR4.5]) has not been established. In clinical studies, treatment with SPRYCEL in pediatric patients with Ph+ ALL was administered for a maximum duration of 2 years [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

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#### 5.1 Myelosuppression
- Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML.
- In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated. (…)
- In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery. (…)

#### 5.2 Bleeding-Related Events
- In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction in vitro. In all CML or Ph+ ALL clinical studies, 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 2398 patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2712 SPRYCEL-treated patients was 19.2 months (range 0.93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1618 patients with chronic phase CML was 29 months (range 0.9–9.2 months). The median duration of therapy in 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0.9–9.2 months). (…)
- (…) In the randomized trial in patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 39%. Among the 1618 SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to 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 0.3–31 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 multiagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL. (See Clinical Studies (14.4)). The median duration of therapy was 24 months (range 2 to 27 months). (See Tables 14 and 15) (…)

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.4 Pediatric Use

#### Ph+ CML in Chronic Phase
- The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML. (See Clinical Studies (14.3)). There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of patients (see Warnings and Precautions (5.10)).
- Ph+ ALL
- The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported.
- The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects (see Adverse Reactions (6.1) and Clinical Studies (14.3, 14.4)).
- Monitor bone growth and development in pediatric patients (see Warnings and Precautions (5.10)).
- Pediatric Patients with Difficulty Swallowing Tablets
- Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. (…)

#### 14 CLINICAL STUDIES

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<td>01037/1/02/06/2018</td>
<td>Denileukin Diftitox</td>
<td>Oncology</td>
<td>IL2RA (CD25 antigen)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>Ontak is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.</td>
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<td>014399, 11/09/2018</td>
<td>Desipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>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 7-10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).</td>
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<td>020118, 03/01/2019</td>
<td>Desflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS The use of SUPRANE is contraindicated in the following conditions: • Known or suspected genetic susceptibility to malignant hyperthermia.</td>
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<tr>
<td>021992, 02/06/2018</td>
<td>Desvenlafaxine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and elimination. Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoenzymes) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 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.</td>
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<td>208082, 06/06/2018</td>
<td>Deutetrabenzine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions</td>
<td>2 DOSAGE AND ADMINISTRATION 2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers In patients who are poor CYP2D6 metabolizers, the total daily dosage of ALUSTEDO should not exceed 36 mg (maximum single dose of 18 mg).</td>
</tr>
</tbody>
</table>

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 06/2020

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<th>Biomarker†</th>
<th>Labeling Sections</th>
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<td>Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td>[see Use in Specific Populations (8.7)].</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.7 QTc Prolongation</td>
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<td>(...) 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)]. (...)</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.7 Poor CYP2D6 Metabolizers</td>
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<td>Although the pharmacokinetics of deutetabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similarly to taking a strong CYP2D6 inhibitor (approximately 3-fold). In patients who are CYP2D6 poor metabolizers, the daily dose of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Poor CYP2D6 Metabolizers</td>
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<td>Although the pharmacokinetics of deutetabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similarly to taking a strong CYP2D6 inhibitors (approximately 3-fold) [see Dosage and Administration (2.4), Drug Interactions (7.1)].</td>
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**022287, 06/07/2018**  
**Dexlansoprazole**  
**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.

**12 CLINICAL PHARMAOCOLOGY**  
**12.3 Pharmacokinetics**  
**Metabolism**  
 (...) CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates: extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.  
**Cytochrome P 450 Interactions**  
(...) Although in vitro studies indicated that DEXILANT has the potential to inhibit CYP2C19 in vivo, an in vivo drug-drug interaction study in mainly CYP2C19 extensive and intermediate metabolizers has shown that DEXILANT does not affect the pharmacokinetics of diazepam (CYP2C19 substrate). (...)  
**Clopidogrel**  
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with DEXILANT 60 mg capsules (n=40), for nine days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 86-97%) when DEXILANT was co-administered compared to administration of clopidogrel alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The effect on exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important.  
**12.5 Pharmacogenomics**  
**Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole**  
Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of DEXILANT 60 mg or control tablets (N=2 to 6 subjects/group), mean dexlansoprazole 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 dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

**021879, 06/11/2019**  
**Dextromethorphan and Quinidine**  
**Neurology**  
**CYP2D6**  
**Warnings and Precautions, Clinical Pharmacology**  
**5 WARNINGS AND PRECAUTIONS**  
**5.4 Concomitant use of CYP2D6 Substrates**  
The quinidine component of NUDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUDEXTA that are metabolized by CYP2D6 [see Drug Interactions (7.5)].  
**5.8 CYP2D6 Poor Metabolizers**  
The quinidine component of NUDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3), (12.5)]. Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of
NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin), crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcT were 5.6 ms for dextromethorphan 30 mg/quinidine 10 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype.

12.3 Pharmacokinetics
Metabolism and Excretion
NUEDEXTA is a combination product containing dextromethorphan and quinidine. Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. After dextromethorphan 300 mg/quinidine 30 mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours. (…)

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

020648, 12/16/2016
Diazepam
Neurology
CYP2C19
Clinical Pharmacology
12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism and Elimination
(…)

12.5 Pharmacogenomics
(…)

125518, 03/01/2017
Dinutuximab
Oncology
MYCN
Clinical Studies
14 CLINICAL STUDIES
(…)

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

204790, 09/06/2018
Dolutegravir
Infectious Diseases
UGT1A1
Clinical Pharmacology
12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism and Elimination
Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). (…)

020690, 12/18/2018
Donepezil
Neurology
CYP2D6
Clinical Pharmacology
12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of 14C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-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.

020238, 03/17/2010
Doxepin (1)
Psychiatry
CYP2D6
Clinical Pharmacology
12 CLINICAL PHARMACOLOGY
12.5. Special Population
Poor Metabolizers of CYPs
Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.

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<th>Therapeutic Area*</th>
<th>Biomarker‡</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</table>
| 02/20/86     | 03/17/2010                 | Doxepin (2)        | Psychiatry        | CYP2C19    | Clinical Pharmacology      | 12 CLINICAL PHARMACOLOGY  
12.5. Special Population  
Poor Metabolizers of CYPs  
Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects. |
| 205525       | 09/14/2018                 | Dronabinol         | Gastroenterology  | CYP2C9     | Use in Specific Populations, Clinical Pharmacology | 8 USE IN SPECIFIC POPULATIONS  
8.6 Effect of CYP2C9 Polymorphism  
Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function [see Clinical Pharmacology (12.5)]. |
| 02/16/76     | 08/08/2017                 | Drospirenone and Ethinyl Estradiol | Gynecology | CYP2C19    | Clinical Pharmacology      | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Effects of Combined Oral Contraceptives on Other Drugs  
(…) In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. (…) |
| 03/14/17     | 12/19/2017                 | Duloxetine         | Psychiatry        | CYP2D6     | Drug Interactions          | 7 DRUG INTERACTIONS  
7.3 Dual Inhibition of CYP1A2 and CYP2D6  
Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax. |
| 76/1069      | 06/05/2020                 | Durvalumab         | Oncology          | CD274 (PD-L1) | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Specific Populations  
Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance (CLcr) 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN and bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status had no clinically significant effect on the pharmacokinetics of durvalumab. (…) |
| 2115/55      | 09/26/2019                 | Duvelisib          | Oncology          | Chromosome 17p | Clinical Studies          | 14 CLINICAL STUDIES  
14.1 Efficacy in Relapsed or Refractory CLL/SLL  
Study 2  
(…) In this subset (95 randomized to COPIKTRA, 101 to ofatumumab), the median patient age was 69 years (range: 40 to 90 years), 59% were male, and 88% had an ECOG performance status of 0 or 1. Forty-six percent received 2 prior lines of therapy, and 54% received 3 or more prior lines. At baseline, 52% of patients had at least one tumor ≥ 5 cm, and 22% of patients had a documented 17p deletion. (…) |
| 12/5166      | 06/20/2017                 | Eculizumab (1)     | Neurology         | ACHR       | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE  
1.3 Generalized Myasthenia Gravis (gMG)  
Soliris is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. |

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| Eculizumab                 | Neurology        | AQP4      | Indications and Usage, Clinical Studies    | 1 INICATIONS AND USAGE
1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)
Sorobis 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 Sorbix for the treatment of NMOSD was established in NMOSD Study 1 (NCT01892345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening:
1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening.
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid).
3. On immunosuppressive therapy (IST), on a stable dose regimen.
4. The use of concurrent corticosteroids was limited to 20 mg per day or less.

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<td>Elexacaftor, ivacaftor, and Tezacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>14.4 Clinical Trial in Subjects with Genotype 1 HCV and Severe Renal Impairment including Subjects on Hemodialysis (C-SURFER) C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m²) or CKD Stage 5 (eGFR&lt;15 mL/min/1.73 m²), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or PegIFN a RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: EBR 50 mg once daily + GZR 100 mg once daily for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR + GZR for 12 weeks (deferred treatment group). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive pharmacokinetic [PK]) group. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; and 72% had non-CCC IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.</td>
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<td>Eliglustat</td>
<td>Inborn Errors of Metabolism</td>
<td>CYP2D6</td>
<td>Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test [see Dosage and Administration (2.1)]. Limitations of Use: • Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect [see Clinical Studies (14)]. • A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) [see Clinical Studies (14)]. 2 DOSE ADMINISTRATION 2.1 Patient Selection Select patients with Gaucher disease type 1 based on their CYP2D6 metabolic phenotype. It is recommended patient genotypes be established using an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation. The safety and effectiveness of TRIKAFTA in patients with CF younger than 12 years of age have not been established.</td>
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12.3 Pharmacokinetics

Absorption
The oral bioavailability of eliglustat was less than 5% in CYP2D6 EMs following a single 84 mg dose of CERDELGA. In CYP2D6 EMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose-proportional manner over the dose range of 42 to 256 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-∞)) increased up to about 2-fold at steady state compared to after the first dose (AUC(0-7)). 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 AUC(0-24h) in PMs using a physiologically based pharmacokinetic (PBPK) model with 84 mg once daily were 75 ng/mL and 956 hr ng/mL, respectively.

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, mostly Caucasian, including those of Ashkenazi Jewish descent; however, it included the following populations: African American, American Indians, Hispanics, and Asians, or body weight (41 to 136 kg).

Patients with 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
Eliglustat terminal 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.

Steady-state pharmacokinetics of eliglustat in CYP2D6 EMs and PMs with mild and moderate hepatic impairment is unknown [see Use in Specific Populations (8.7)].

Drug Interactions
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 ritampin (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.

Table 9 describes the effect of drug interactions on the pharmacokinetics of eliglustat [see Drug Interactions (7.1)]. (See Table 9)

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

Effect of other drugs on CERDELGA
CYP2D6 substrates
Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage), metoprolol (a CYP2D6 substrate) mean Cmax and AUC increased by 1.7-fold and 2.3-fold in CYP2D6 EMs, respectively, and by 1.2-fold and 1.6-fold in IMs, respectively [see Drug Interactions (7.2)].

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

14 CLINICAL STUDIES

(…) The CERDELGA treatment group was comprised of IM (5%), EM (80%) and URM (5%) patients. (…)

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<td>022291, 04/29/2020</td>
<td>Eltrombopag (1)</td>
<td>Hematology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS Thrombotic/Thromboembolic Complications Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease), (...)</td>
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<tr>
<td>022291, 04/29/2020</td>
<td>Eltrombopag (2)</td>
<td>Hematology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS Thrombotic/Thromboembolic Complications Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease), (...)</td>
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<tr>
<td>022291, 04/29/2020</td>
<td>Eltrombopag (3)</td>
<td>Hematology</td>
<td>Chromosome 7</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Cytogenetic Abnormalities In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M8 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality: 7 patients had the loss of chromosome 7; 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA. (...) 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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<tr>
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<td>Hematology</td>
<td>Chromosome 13</td>
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<td>761107, 11/20/2018</td>
<td>Emapalumab-tzsg</td>
<td>Hematology</td>
<td>PRF1, RAB27A, SH2D1A, STXB2P, STX11, UNC13D, XIAP (Hemophagocytic Lymphohistiocytosis)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (... 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 (19%), 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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<th>Labeling Text‡</th>
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| 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.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The potential for QTc prolongation with enasidenib was evaluated in an open-label study in patients with advanced hematologic malignancies with an IDH2 mutation. Based on the QTc data for a single dose of 30 mg to 650 mg and multiple doses of 100 mg daily in the fasted state, no large mean changes in the QTc interval (>20 ms) were observed following treatment with enasidenib.

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) (…) Efficacy 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) (…) |

| 210496, 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 BRAFV600E (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.

2.2 Recommended Dosage for BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
The recommended dosage of BRAFV600E 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 BRAFV600E is 300 mg (four 75 mg capsules) orally once daily incombination 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
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<td>Encorafenib (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.5 Dosage Modifications for adverse reactions</td>
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<td>BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma and BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)</td>
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<td>Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 3.</td>
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| 761137, 12/18/2019                      | Entrectinib (2) | Oncology       | NTRK      | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 14 CLINICAL STUDIES
14.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
BRAFV600E mutation-positive metastatic colorectal cancer (CRC) was detected using the Qiagen therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit. In the presence of BRAF V600E mutation in tumor tissue, BRAFV600E was confirmed in solid tumors. In the presence of BRAF V600E mutation, BRAFV600E was confirmed in solid tumors. (See Table 7)

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
ROS1 gene fusions were present in 42% and NTRK gene fusions were present in 20%. Most adults (75%) received ROZLYTREK 600 mg orally once daily. (See Table 7)

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The pharmacokinetics for entrectinib and its pharmacologically active major circulating metabolite M5 were characterized in adult patients with ROS1-positive NSCLC. (See Clinical Table 7)

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
The pharmacokinetics for entrectinib was evaluated in a pooled subgroup of patients with ROS1-positive metastatic NSCLC who received ROZLYTREK at various doses 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-STARTRK-1 (NCT02987810) and STARTRK-2 (NCT02656279). To be included in this pooled subgroup, patients were required to have histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG performance status 0 or 1, and prior therapy with a ROS1 inhibitor. Identification of ROS1 gene fusion in tumor specimens was prospectively determined in local laboratories using either a fluorescent in situ hybridization (FISH) or next-generation sequencing (NGS) laboratory-developed test. All patients were assessed for CNS lesions at baseline. (See Table 7)

14 CLINICAL STUDIES
14.1 ROS1-Positive Non-Small Cell Lung Cancer
The efficacy of ROZLYTREK was evaluated in a pooled subgroup of patients with ROS1-positive metastatic NSCLC who received ROZLYTREK at various doses and schedules (96% received ROZLYTREK 600 mg orally once daily) and were enrolled in one of three multicenter, single-arm, open-label clinical trials: ALKA-STARTRK-1 (NCT02987810) and STARTRK-2 (NCT02656279). To be included in this pooled subgroup, patients were required to have histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG performance status 0 or 1, and prior therapy with a ROS1 inhibitor. Identification of ROS1 gene fusion in tumor specimens was prospectively determined in local laboratories using either a fluorescent in situ hybridization (FISH) or next-generation sequencing (NGS) laboratory-developed test. All patients were assessed for CNS lesions at baseline. (See Table 7)

12 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) who are positive for ROS1

1.2 NTRK Gene Fusion-Positive Solid Tumors
ROZLYTREK is indicated for the treatment of adult 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 durability of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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| 212018, 04/02/2020                     | Erdafitinib (1) | Oncology | FGFR       | Clinical Pharmacology, Clinical Studies | 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.
2.2 Recommended Dosage for NTRK Gene Fusion-Positive Solid Tumors
Adults
The recommended dosage of ROZLYTREK in adults is 600 mg orally once daily or with food until disease progression or unacceptable toxicity.

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

8.4.6 Patient Selection
Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA (see Dosage and Administration (2.1) and Clinical Studies (14)).

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 (NCT02097810) and STARTRK-2 (NCT02568267). To be included in this pooled subgroup, patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease; measurable disease per RECIST v1.1; at least 6 months of follow-up after the first dose of ROZLYTREK; and no prior therapy with a TRK inhibitor. Patients received ROZLYTREK at various doses and schedules (94% received ROZLYTREK 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. (...)

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. (...)

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<th>Biomarker†</th>
<th>Labeling Sections</th>
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</table>

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). Patients were treated with BALVERSA at 8 mg orally once daily; with a dose increase to 9 mg in patients with phosphate levels <9.5 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 Metastatic Breast Cancer

14.1.1 Locally Advanced or Metastatic Breast Cancer (NSCLC) TARCEVA® is indicated for:

1.1 Non-Small Cell Lung Cancer (NSCLC)

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA® is indicated for:

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>Oncology</th>
<th>Biomarker</th>
<th>Use in Specific Populations, Clinical Pharmacology</th>
<th>8 USE IN SPECIFIC POPULATIONS</th>
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<tr>
<td>21/02/18</td>
<td>Erdafitinib</td>
<td>Oncology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
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<td>04/12/2019</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.

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 diaphoresis, anorexia, dyspepsia, and increased appetite. In TARCEVA-treated patients the median time to onset of rash was 15 days and the median time to onset of diaphoresis 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 = 86) or four cycles of a standard platinum-based doublet chemotherapy (n = 88); standard chemotherapy regimens were cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. Randomization was stratified by EGFR mutation (exon 19 deletion or exon 21 (L858R) substitution) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1 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. (…)

(….) The disease characteristics were 93% Stage IV and 7% Stage IIIb with pleural effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition). 93% adenocarcinoma, 66% exon 19 mutation deletions and 34% exon 21 (L858R) point mutation by CTA. (…) In exploratory subgroup analyses based on EGFR mutation subtype, the hazard ratio (HR) for PFS was 0.27 (95% CI 0.17 to 0.43) in patients with exon 19 deletions and 0.52 (95% CI 0.29 to 0.95) in patients with exon 21 (L858R) substitution. The HR for OS was 0.94 (95% CI 0.57 to 1.54) in the exon 19 deletion subgroup and 0.95 (95% CI 0.58 to 1.76) in the exon 21 (L858R) substitution subgroup.

14.2 NSCLC - Lack of Efficacy of TARCEVA in Maintenance Treatment of Patients without EGFR Mutations
Lack of efficacy of TARCEVA for the maintenance treatment of patients with NSCLC without EGFR activating mutations was demonstrated in Study 2. Study 2 was a multicenter, placebo-controlled, randomized trial of 643 patients with advanced NSCLC without an EGFR exon 19 deletion or exon 21 L858R mutation who had not experienced disease progression after four cycles of platinum-based chemotherapy. (…) Determination of EGFR mutation status was not required for enrollment. (…) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition), 93% adenocarcinoma including bronchioloalveolar (45%), squamous (40%) and large cell (5%) and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…)

6 ADVERSE REACTIONS
6.1 Clinical Trials 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 diaphoresis, anorexia, dyspepsia, and increased appetite. In TARCEVA-treated patients the median time to onset of rash was 15 days and the median time to onset of diaphoresis was 32 days. (…)

7 DRUG INTERACTIONS
7.19 Drugs Metabolized by Cytochrome P450 2C9
In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2C9. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2C9 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2C9, is unlikely to have clinically significant effects on escitalopram metabolism. (…)

(….) In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2C9. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2C9 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2C9, is unlikely to have clinically significant effects on escitalopram metabolism. (…)

7.2 Pharmacokinetics
7.2.7 Effect of Drug Interactions
- Concomitant administration of escitalopram with drugs that induce CYP3A4 (e.g., rifampin) may lead to decreased escitalopram serum levels.
- Concomitant administration of escitalopram with drugs that inhibit CYP3A4 (e.g., ketoconazole) may lead to increased escitalopram serum levels.

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<td>210132, 10/28/2018</td>
<td>Eteplirsen</td>
<td>Neurology</td>
<td>DMD</td>
<td>4 CONTRAINdications</td>
<td>BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are contraindicated in women with any of the following conditions:</td>
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<td>• Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders</td>
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<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (1)</td>
<td>Gynecology</td>
<td>PROC</td>
<td>4 CONTRAINdications</td>
<td>BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are contraindicated in women with any of the following conditions:</td>
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<td>Estradiol and Progesterone (2)</td>
<td>Gynecology</td>
<td>PROS1</td>
<td>4 CONTRAINdications</td>
<td>BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are contraindicated in women with any of the following conditions:</td>
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<td>210132, 10/28/2018</td>
<td>Estradiol and Progesterone (3)</td>
<td>Gynecology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>4 CONTRAINdications</td>
<td>BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are contraindicated in women with any of the following conditions:</td>
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<td>• Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders</td>
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| 206488, 10/11/2018                     | Everolimus (1) | Oncology | ERBB2 (HER2) | 1 INDICATIONS AND USAGE | EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. (…)
|                                        |      |                  |            |                  | 4 CONTRAINdications | 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 |

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</table>
| 022334, 02/13/2020                     | Everolimus (2) | Oncology | ESR (Hormone Receptor) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 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, HER2 2+ (negative) advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Table 20 and Figure 1) (…) 6 USE IN SPECIFIC POPULATIONS Other Indications
    - (…) 8.5 Geriatric Use
      - In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study (BOLERO-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 < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [see Dosage and Administration (2.9), Use in Specific Populations (8.5)]. 12 CLINICAL PHARMACOLOGY 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 (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (28 to 93 years), and 75% were White. The median follow-up was approximately 13 months. (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. (…) |
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<td>761139, 12/20/2019</td>
<td>Pam-Trastuzumab Deruxtecan-nxki</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.</td>
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<tr>
<td>020753, 05/18/2018</td>
<td>Exemestane</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Adjuvant Treatment of Postmenopausal Women AROMASIN is indicated for adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy.</td>
</tr>
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1.3 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/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Table 20 and Figure 1) (…) 14.2 Advanced Refractory Malignancies A randomized, double-blind study comparing exemestane plus AFINITOR versus exemestane plus placebo was conducted in 121 patients with advanced refractory malignancies who had failed one or more prior treatments. (…) 14.3 Endocrine Therapy Resistance 14.3.1 Advanced Breast Cancer 14.3.2 Refractory Malignancies 14.4 Other Tumor Types In a randomized, open-label trial comparing AFINITOR plus letrozole versus letrozole plus placebo, 182 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer were evaluated. (…) 14.5 Other 14.5.1 Advanced Breast Cancer 14.5.2 Refractory Malignancies 14.5.3 Other Tumor Types 14.5.4 Other 14.6 Endocrine Therapy Resistance 14.6.1 Advanced Breast Cancer 14.6.2 Refractory Malignancies 14.6.3 Other Tumor Types 14.6.4 Other 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. (…) the 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. (…) 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) (…) (…) in the hormone-receptor-positive subpopulation representing about 85% of the trial patients, disease-free survival was also statistically significantly improved (HR = 0.69, 95% CI: 0.53, 0.81, P = 0.00001) in the AROMASIN arm compared to the tamoxifen arm. Consistent results were observed in the subgroups of patients with node negative or positive disease, and patients who had or had not received prior chemothermy. (See Table 9) (…) 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (…) the safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2 positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201 A-J101 (NCT02564900). ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31). (…) 6.2 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, two cases (0.9%) of asymptomatic LVEF decrease were reported. (…) 6.3 Left Ventricular Dysfunction Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. (…) 7.1 Safety and Tolerability 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 or 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

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<td>022030, 11/21/2017</td>
<td>Flibanserin (2)</td>
<td>Gynecology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>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. &gt;20 ms) on the QTc interval in an open label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.</td>
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<tr>
<td>022526, 08/18/2015</td>
<td>Flibanserin (1)</td>
<td>Gynecology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>The efficacy of ENHERTU was evaluated in study DESTINY-Breast01 (NCT03248492), a multicenter, single-arm, trial that enrolled 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients were excluded for a history of treated ILD or current ILD at screening. Patients were also excluded for history of clinically significant cardiac disease, active brain metastases, and ECOG performance status &gt;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.</td>
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<td>022526, 08/18/2015</td>
<td>Flibanserin (3)</td>
<td>Gynecology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>In a pharmacogenomic study of 100 mg ADDY1 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)).</td>
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<tr>
<td>020985, 12/16/2003</td>
<td>Fluorouracil (1)</td>
<td>Dermatology</td>
<td>DPYD</td>
<td>Contraindications, Warnings</td>
<td>CONTRAINDICATIONS:…Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydroxypyrimidine 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. Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parental administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase “DPD” activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topicaly applied fluorouracil. Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.</td>
</tr>
<tr>
<td>012209, 07/29/2016</td>
<td>Fluorouracil (2)</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS: 5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase (DPD) Activity: Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and 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>
</tr>
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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 Drug Interactions Drugs metabolized by CYP2D6: Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Co-administration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and butyrophenones), and antihistamines (e.g., propafenone, fexofenadine, 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., fexofenadine, 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>018708, 05/09/2016</td>
<td>Flurbiprofen</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Poor Metabolizers of CYP2C9 Substrates In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.</td>
</tr>
<tr>
<td>018554, 07/23/2001</td>
<td>Flutamide</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNINGS Aniline Toxicity: One metabolite of flutamide is 4-nitro-3-fluoromethylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (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>02007, 05/29/2019</td>
<td>Formoterol (1)</td>
<td>Pulmonary</td>
<td>CYP2D6</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 CYP19 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>
</tr>
<tr>
<td>02007, 05/29/2019</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 CYP19 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>
</tr>
<tr>
<td>020450, 10/31/2017</td>
<td>Phosphenytoin</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Serious Dermatologic Reactions Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin (the active metabolite of CEREBYX) treatment. The onset of symptoms is usually within 28 days, but can occur later. CEREBYX should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see Warnings and Precautions (5.5)). Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA B<em>1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA B</em>1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding CEREBYX as an alternative for carbamazepine patients positive for HLA B*1502.</td>
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<td>022033, 01/04/2017</td>
<td>Fluvoxamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td></td>
</tr>
<tr>
<td>021344, 05/13/2020</td>
<td>Fulvestrant (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td></td>
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The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

7 DRUG INTERACTIONS
7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes
(…)

1 INDICATIONS AND USAGE
1.1 Monotherapy
FASLODEX is indicated for the treatment of:
• HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
• HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.

1.2 Combination Therapy
FASLODEX is indicated for the treatment of:
• Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or
• HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.

2 ADVERSE REACTIONS
2.1 Clinical Trials Experience
Combination Therapy
The safety of FASLODEX 500 mg plus palbociclib in 6299 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least one dose of FASLODEX plus palbociclib or placebo in MONARCH 2 (NCT02107703) was assessed. The safety of FASLODEX 500 mg plus palbociclib in 645 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus palbociclib or placebo in MONALEESA-3 (NCT-1942135) was assessed. The safety of FASLODEX 500 mg plus abemaciclib in 345 out of 517 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (…)

3 DRUG INTERACTIONS
3.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes
(…)

6.1 Clinical Trials Experience
Combination Therapy
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 one dose of FASLODEX plus palbociclib or placebo in MONARCH 2. (…)

6.2 Clinical Trials Experience
Combination Therapy
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. (…)

6.3 Clinical Trials Experience
Combination Therapy
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 15.6 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (…)

6.4 Clinical Trials Experience
Combination Therapy
The safety of FASLODEX 500 mg plus abemaciclib 150 mg versus FASLODEX plus placebo was evaluated in MONARCH 2. The data described below reflect exposure to FASLODEX plus abemaciclib in 286 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (…)

7 CLINICAL STUDIES
7.1 Clinical Trials Experience
Combination Therapy
The safety of FASLODEX 500 mg plus palbociclib in 645 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus palbociclib or placebo in MONALEESA-3. Median duration of treatment was 15.6 months for FASLODEX plus palbociclib and 12 months for FASLODEX plus placebo. (…)

8 CLINICAL STUDIES
8.1 Clinical Trials Experience
Combination Therapy
The safety of FASLODEX 500 mg plus abemaciclib in 345 out of 517 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (…)

9 CLINICAL STUDIES
9.1 Clinical Trials Experience
Combination Therapy
The safety of FASLODEX 500 mg 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 15.6 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (…)

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

**6 ADVERSE REACTIONS**

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

Combination Therapy
Combination Therapy with Palbociclib (PALOMA-3):
The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months. (...)

Combination Therapy with Abemaciclib (MONARCH 2):
The safety of FASLODEX (500 mg) plus abemaciclib (150 mg twice daily) versus FASLODEX plus placebo was evaluated in MONARCH 2. The data described below reflect exposure to FASLODEX in 664 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (...)

Combination Therapy with Ribociclib (MONALEESA-3):
The safety of FASLODEX 500 mg plus ribociclib 600 mg versus FASLODEX plus placebo was evaluated in MONALEESA-3. The data described below reflect exposure to FASLODEX plus ribociclib in 483 out of 724 postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy who received at least one dose of FASLODEX plus ribociclib or placebo in MONALEESA-3. Median duration of treatment was 15.8 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (...)

**12 CLINICAL PHARMACOLOGY**

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

**14 CLINICAL STUDIES**

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 postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (...)

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

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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 3 H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 38-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average. (…)  
(…) RAZADYNE® ER 24 mg extended-release capsules administered once daily under fasting conditions are bioequivalent to RAZADYNE® tablets 12 mg twice daily with respect to AUC24h and Cmin. The Cmax and Tmax of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with Cmax about 25% lower and median Tmax occurring about 4.5–5.0 hours after dosing. Dose proportionality is observed for 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 and Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by a 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](http://www.fda.gov/CompanionDiagnostics).  
14 CLINICAL STUDIES  
Non-Small Cell Lung Cancer (NSCLC)  
Study 1  
The efficacy and safety of IRESSA for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or L858R substitution mutations was demonstrated in a multicenter, single-arm, open-label clinical study (Study 1). A total of 106 treatment-naive patients with metastatic EGFR mutation positive NSCLC received IRESSA at a dose of 250 mg once daily until disease progression or intolerable toxicity. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by both a Blinded Independent Central Review (BICR) and investigators. Duration of response (DOR) was an additional outcome measure. Eligible patients were required to have a deletion in EGFR exon 19 or L858R, L861Q, or G719X substitution mutation and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. Tumor samples from 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 (48%), WHO PS 2 (7%), and adenocarcinoma histology (97%). Sixty patients had exon 19 deletions (65%), 29 patients had L858R substitution (31%), while two patients each had tumors harboring L861Q or G719X substitution mutation. The median duration of treatment was 8.0 months. (See Table 3)  
The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation with duration of response of at least 2.8 months and 5.6 months, respectively. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response with duration of response of at least 2.8 months.  
Study 2 |

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| 206995, 08/22/2018                      | Gefitinib (2) | Oncology | CYP2D6 | Clinical Pharmacology | 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. (…)

12 CLINICAL PHARMACOLOGY
CYP2D6 Poor metabolizer
CYP2D6 metabolizes gefitinib to O-desmethyl gefitinib in vitro. In healthy CYP2D6 poor metabolizers, O-desmethyl gefitinib concentration was not measurable and the mean exposure to gefitinib was 2-fold higher as compared to the extensive metabolizers. This increase in exposure in CYP2D6 poor metabolizers may be clinically important because some adverse drug reactions are related to higher exposure of gefitinib. No dose adjustment is recommended in patients with a known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse reactions. The impact of CYP2D6 inhibiting drugs on gefitinib pharmacokinetics has not been evaluated. However, similar precautions should be used when administering CYP2D6 inhibitors with IRESSA because of the possibility of increased exposure in these patients. An exploratory exposure response analysis showed an increase in the incidence of interstitial lung disease (ILD) with a greater than 2 fold increase in the gefitinib exposure [see Warnings and Precautions (5.1)].

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. (…)
Monotherapy for Newly-Diagnosed CD33-positive AML
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)]. (…)
Monotherapy for Relapsed or Refractory CD33-positive AML
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. (…)

14 CLINICAL STUDIES
14.1 Newly-Diagnosed CD33-positive AML
Study ALFA-0701
CD33 expression on AML blasts by flow cytometry harmonized from local laboratory results was determined in 194/271 (72%) patients overall. Few patients (14%) had low CD33 expression (less than 30% of blasts), and none had no expression of CD33. (…)

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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 1.1 Relapsed or Refractory Acute Myeloid Leukemia XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.</td>
</tr>
<tr>
<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 14.1 Relapsed or Refractory Acute Myeloid Leukemia 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, DB35, or D36 mutation by the LeukoStrat CDx FLT3 Mutation Assay. (See Table 4) (…). For patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only. (See Table 6) (…). In the final analysis, the CR/CRh 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/CRh, the median time to first response was 2 months (range, 0.9 to 9.6 months). The CR/CRh 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>
</tr>
<tr>
<td>020496, 12/21/2018</td>
<td>Glimepiride</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.3 Hemolytic Anemia Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving AMARYL, who did not have known G6PD deficiency (see Adverse Reactions [6.2]).</td>
</tr>
<tr>
<td>017783, 06/18/2016</td>
<td>Glipizide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Hemolytic Anemia Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylureas can lead to hemolytic anemia. Because GLUCOTROL belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.</td>
</tr>
<tr>
<td>020051, 08/22/2017</td>
<td>Glyburide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Hemolytic Anemia Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylureas can lead to hemolytic anemia. Because GLYNASE PresTab belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea 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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<tr>
<td>211970, 12/12/2019</td>
<td>Golodirsen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Use in</td>
<td>1 INDICATIONS AND USAGE 1.1 Nonspecific Nonspecific 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.</td>
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<td>019726, 02/12/2015</td>
<td>Goserelin</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>VYONDYS 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53 [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.</td>
</tr>
<tr>
<td>020727, 03/12/2019</td>
<td>Hydralazine</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
<td>1 INDICATIONS AND USAGE 1.5 Advanced Breast Cancer ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women. The estrogen and progesterone receptor values may help to predict whether ZOLADEX therapy is likely to be beneficial [see Dosage and Administration (2.6), Clinical Pharmacology (12.1), and Clinical Studies (14.5)].</td>
</tr>
<tr>
<td>009768, 01/27/2017</td>
<td>Hydroxychloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS (…) PLAQUENIL should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…)</td>
</tr>
<tr>
<td>205552, 04/21/2020</td>
<td>Brutinib (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>
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<td>205552, 04/21/2020</td>
<td><strong>Ibrutinib</strong> (2)</td>
<td>Oncology</td>
<td>Chromosome 11q</td>
<td>Clinical Studies</td>
<td><strong>14 CLINICAL STUDIES</strong>&lt;br&gt;14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma&lt;br&gt;<strong>RESONATE-2</strong>&lt;br&gt;(…) The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%).&lt;br&gt;(…) <strong>HELIOS</strong>&lt;br&gt;(…) The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor &gt; 5 cm and 28% presented with del11q. (…) The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy included: lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%). (…) In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].</td>
</tr>
<tr>
<td>205552, 04/21/2020</td>
<td><strong>Ibrutinib</strong> (3)</td>
<td>Oncology</td>
<td>MYD88</td>
<td>Clinical Studies</td>
<td><strong>14 CLINICAL STUDIES</strong>&lt;br&gt;14.3 Waldenström’s Macroglobulinemia&lt;br&gt;<strong>INNOVATE</strong>&lt;br&gt;(…) 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 14% of patients, and 9% of patients were not evaluable for mutation status. (…)</td>
</tr>
<tr>
<td>022192, 02/23/2017</td>
<td><strong>Iloperidone</strong></td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td><strong>2 DOSAGE AND ADMINISTRATION</strong>&lt;br&gt;2.2 Dosage in Special Populations&lt;br&gt;Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6&lt;br&gt;FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 [see Clinical Pharmacology (12.3)].</td>
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<td>021588, 08/21/2018</td>
<td>Imatinib (1)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3-4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4. Metabolism and Elimination Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P86 and P88. The iloperidone metabolite P86 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. Approximately 7% - 10% of Caucasians and 3% - 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers. Coadministration of FANAPT with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3- fold increase in iloperidone plasma exposure, and therefore one-half of the FANAPT dose should be administered. Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs. The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.</td>
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<td>021588, 08/21/2018</td>
<td>Imatinib (2)</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>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. (…)</td>
</tr>
</tbody>
</table>

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)

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

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

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

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

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

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

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

2 DOSAGE AND ADMINISTRATION

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

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

2.2 Pediatric Patients with Ph+ CML CP

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

2.3 Adult Patients with Ph+ ALL

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

2.4 Adult Patients with Ph+ ALL

The recommended dose of Gleevec is 400 mg/day for adult patients with relapsed/refractory Ph+ ALL.

2.5 Pediatric Patients with Ph+ ALL

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

2.14 Dose Adjustment for Hematologic Adverse Reactions

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

5 WARNINGS AND PRECAUTIONS

5.1 Fluid Retention and Edema

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

5.3 Congestive Heart Failure and Left Ventricular Dysfunction

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

5.5 Hemorrhage

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

6 ADVERSE REACTIONS

6.1 Chronic Myeloid Leukemia

The majority of Gleevec-treated patients experienced adverse reactions at some time. Gleevec was discontinued due to drug-related adverse reactions in 2.4% of patients receiving Gleevec in the randomized trial of newly diagnosed patients with Ph+ CML in chronic phase comparing Gleevec versus IFN+Ara-C, and in 12.5% of 750,000/mL) and thrombocytopenia (less than 75,000/mL). In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

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

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on the trial who did not receive Gleevec. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Gleevec. The protocol included up to 18 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Gleevec and 647 without Gleevec. The adverse events that were reported with a 5% or greater incidence in patients with Ph+ ALL compared to Ph- ALL or with a 1% or greater incidence in cycles of therapy that included Gleevec are presented in Table 8. (See Table 8) (…)

### 6.4 Acute Lymphoblastic Leukemia

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

### 6.7 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The safety profile in the HES/CML 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+Gleevec) has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (See Table 18) (…) An open-label, multicenter, randomized trial (Gleevec versus nilotinib) was conducted to determine the efficacy of Gleevec versus nilotinib in adult patients with cytogenetically confirmed, newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. (See Table 19) (…) Late Chronic Phase CML and Advanced Stage CML: Three international, open-label, single-arm phase 2 studies were conducted to determine the safety and efficacy of Gleevec in patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were black. In clinical studies, 38%-40% of patients were ≥60 years of age and 10%-12% of patients were ≥70 years of age. (…) Chronic Phase, Prior Interferon-Alpha Treatment: Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). (…) **14.2 Pediatric CML**

One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. (…) In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day. **14.3 Acute Lymphoblastic Leukemia**

A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease were studied, 43 of whom received the recommended Gleevec dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL received Gleevec 600 mg/day in a phase 1 study. Confirmed and unconfirmed hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 21. The median duration of hematologic response was 3.4 months and the median duration of MCR was 2.3 months. (See Table 21) (…) **14.4 Pediatric ALL**

Pediatric and young adult patients with very high risk ALL, defined as those with an expected 5-year event-free survival (EFS) less than 45%, were enrolled after induction therapy on a multicenter, non-randomized cooperative group pilot protocol. The safety and effectiveness of Gleevec (340 mg/m²/day) in combination with intensive chemotherapy was evaluated in a subgroup of patients with Ph+ ALL. The protocol included intensive chemotherapy and hematopoietic stem cell transplant after 2 courses of chemotherapy for patients with an appropriate HLA-matched family donor. There were 92 eligible patients with Ph+ ALL enrolled. (…) *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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<th>Therapeutic Area*</th>
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<th>Labeling Text‡</th>
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| 021588, 08/21/2018                     | Imatinib (3) | Oncology | PDGFRB | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)  
Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)].  
2 DOSAGE AND ADMINISTRATION  
2.6 Adult Patients with MDS/MPD  
Determine PDGFRB gene rearrangements status prior to initiating treatment. Information on FDA-approved tests for the detection of PDGFRB rearrangements is available at http://www.fda.gov/companiondiagnostics.  
The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.  
14 CLINICAL STUDIES  
14.5 Myelodysplastic/Myeloproliferative Diseases  
14.7 Hyperesinophilic Syndrome/Chronic Eosinophilic Leukemia  
Adult patients with hyperesinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRA fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRA fusion kinase negative or unknown.  
14.8 Dermatofibrosarcoma Protubersans  
Dermatofibrosarcoma Protubersans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22 that results in the fusion of the collagen type 1 alpha 1 gene and the PDGF B gene. An open-label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…). (…) Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. (See Table 25) (…). (…) For the 10 patients with the PDGF B gene rearrangement there were 4 complete and 6 partial responses. The median duration of response in the phase 2 study was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.  
14.6 Aggressive Systemic Mastocytosis  
One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) (…) Sixteen patients had a translocation, involving chromosome 5q33 or 4q12, resulting in a PDGFR gene rearrangement. All of these patients responded hematologically (13 completely). Cytophenic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1 (7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytophenic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8–26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in Table 22. Response durations of phase 2 study patients ranged from 141+ days to 457+ days. (See Table 22).  
14.5 Myelodysplastic/Myeloproliferative Diseases  
14.6 Aggressive Systemic Mastocytosis  
14.7 Hyperesinophilic Syndrome/Chronic Eosinophilic Leukemia  
One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) (…) Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. (See Table 25) (…). (…) For the 10 patients with the PDGF B gene rearrangement there were 4 complete and 6 partial responses. The median duration of response in the phase 2 study was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.  
14.5 Myelodysplastic/Myeloproliferative Diseases  
14.6 Aggressive Systemic Mastocytosis  
2.7 Adult Patients with ASM  
Determine D816V c-Kit mutation status prior to initiating treatment. Information on FDA-approved test for the detection of D816V c-Kit mutation is available at http://www.fda.gov/companiondiagnostics. The recommended dose of Gleevec is 400 mg/day for adult patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRA, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.  
2.8 Adult Patients with HES/CEL  
The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRA fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.  
2.14 Dose Adjustment for Hematologic Adverse Reactions  
Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (…).  
14 CLINICAL STUDIES  
14.6 Aggressive Systemic Mastocytosis  
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### Table of Pharmacogenomic Biomarkers in Drug Labeling
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<thead>
<tr>
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<th>Therapeutic Area†</th>
<th>Biomarker‡</th>
<th>Labeling Sections</th>
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<td>(…)* Seven of these 20 patients had the FIP1L1-PDGFα fusion kinase (or CHIC2 deletion). Patients with this genetic abnormality are predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K506E) and four patients had a D816V c-KIT mutation (not considered sensitive to Gleevec), one with concomitant CML. (See Table 23) (…)* 14.7 Hyper eosinophilic Syndrome/Chronic Eosinophilic Leukemia One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Aki, Kit or PDGFR protein tyrosine kinases. (See Table 24) (…)*</td>
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<tr>
<td>017090, 07/28/2014</td>
<td>Ipsi pramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>Drug Interactions</td>
<td>Drugs Metabolized by P450 2D6</td>
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<td>The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). (…)*</td>
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<tr>
<td>022383, 05/29/2019</td>
<td>Indacaterol</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.4 Pharmacokinetics</td>
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<td>The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7 genotypes (low UGT1A1 expression; also referred to as *28) and the (TA)6, (TA)7 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.</td>
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<tr>
<td>761142, 06/11/2020</td>
<td>Inebilizumab-odon</td>
<td>Neurology</td>
<td>AQP4</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>UPLIZNA is indicated for the treatment of nevromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.</td>
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<tr>
<td>211172, 10/05/2018</td>
<td>Inotersen</td>
<td>Neurology</td>
<td>TTR</td>
<td>6 ADVERSE REACTIONS</td>
<td>6.1 Clinical Trials Experience</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 Va30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different other point mutations. (…)*</td>
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<td>761040, 08/17/2017</td>
<td>Ozogamicin</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>14 CLINICAL STUDIES</td>
<td>14.1 Unresetable or Metastatic Melanoma</td>
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<td>The safety and efficacy of YEVEROY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT009004653) that included 676 randomized patients with unresetable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YEVEROY at 3 mg/kg in combination with an investigational peptide vaccine</td>
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<tr>
<td>125377, 05/26/2020</td>
<td>Ipilimumab [1]</td>
<td>Oncology</td>
<td>HLA-A</td>
<td>14 CLINICAL STUDIES</td>
<td>14.1 Unresetable or Metastatic Melanoma</td>
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<td>Ipilimumab (2)</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
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1 INDICATIONS AND USAGE
1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.4)]. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and 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 (NCT02060188), an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer. (…)

Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer

The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, non-randomized, multiple parallel-cohort trial. 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 (NCT02060188) 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 IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks. Patients enrolled in the single-agent YERVOY 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 14) (…)

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<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.6 Metastatic Non-Small Cell Lung Cancer</td>
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<td>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.</td>
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<td>2 DOSE ADMINISTRATION</td>
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<td>2.1 Patient Selection</td>
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<td>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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a></td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.5 Geriatric Use</td>
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<td>(…) Of the 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received YERVOY with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older [see Clinical Studies (14.6), (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.3 Previously Untreated Advanced Renal Cell Carcinoma</td>
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<td>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. (…)</td>
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<td>(…) The major efficacy outcome measures were OS, PFS (irRC-assessed), and confirmed ORR (irRC-assessed) in intermediate/poor-risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to nivolumab plus YERVOY as compared with sunitinib (Table 19 and Figure 3). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. (…)</td>
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<td>14.6 Metastatic Non-Small Cell Lung Cancer</td>
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<td>First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab</td>
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<td>CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [IASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. (…) Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDX assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). (…)</td>
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<td>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 65 years (range: 26 to 87) with 49% of patients 65 years or older, 10% of patients 75 years or older, 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 YERVOY and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 22 and Figure 4. (See Table 22 and Figure 4)</td>
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<td>First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy</td>
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<td>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. (…)</td>
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<td>Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and paclitaxel 200 mg/m2 for squamous NSCLC or carboplatin (AUC 6) and paclitaxel 200 mg/m2 for non-squamous NSCLC, or carboplatin (AUC 6) and paclitaxel 200 mg/m2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus &lt;1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. (…)</td>
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<td>A total of 719 patients were randomized to receive either YERVOY in combination with nivolumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients 65 years and 10% of patients 75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%). 57% had tumors with PD-L1 expression 11% and 37% had tumors with PD-L1 expression that was ≥1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 85% were former or current smokers. (…)</td>
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</table>
| 125377, 05/26/2020                     | 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 IIEB (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 [IASC]) 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, and 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-816 (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification (IASC)), 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, 05/26/2020                      | Ipilimumab (5) | Oncology | EGFR | 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. |
|                                          |      |                  |            |                   |                |

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 IIA (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-8LA, 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-8LA (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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</table>
| 020571, 01/30/2020                      | Dirnaclam | Oncology | UGT1A1    | Dosage and Administration, Warnings and Precautions, Clinical Pharmacology | 2 DOSEAGE AND ADMINISTRATION

2.3 Dosage in Patients with Reduced UGT1A1 Activity

When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (see Dosage and Administration (2.1 and 2.2) and Warnings and Precautions (5.3)). However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Tables 1-4).

5 WARNINGS AND PRECAUTIONS

5.3 Patients With Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment.

In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m² once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype).

In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m²) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4.5%, and in patients heterozygous for this allele the incidence was 5.3%. Grade 4 neutropenia was observed in 1.8% of patients homozygous for the wild-type allele. In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m²) in combination with budesonide 5-FULV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18.2%, and in patients heterozygous for this allele the incidence was 11.1%. Grade 4 neutropenia was observed in 6.8% of patients homozygous for the wild-type allele.

When administered in combination with other agents or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Dosage and Administration (2)).

UGT1A1 Testing

A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Metabolism

Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In vitro studies indicate that irinotecan, SN-38 and another metabolite ambroxol di-β-carboxylate (APC), do not inhibit cytochrome P-450 isozymes. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1 6/6 genotype, SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro.

A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

14 CLINICAL STUDIES

14.1 Multiple Myeloma

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. (…)

15 CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

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<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
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<td>Isosorbide Dinitrate</td>
<td>Cardiology</td>
<td>CYB5R</td>
<td>Overdosage</td>
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<td>020215, 10/02/2014</td>
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<td>Cardiology</td>
<td>CYB5R</td>
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<td>20318B, 04/28/2019</td>
<td>Ivacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>Ivacaftor</td>
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<td>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 double-blind 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) (…)</td>
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</tbody>
</table>

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 pediatric patients with CF: • 6 to 17 years of age with a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H mutation in the CFTR gene [see Adverse Reactions (6) and Clinical Studies (14)]. • 12 to 17 years of age who are heterozygous for the F508del mutation and a second mutation predicted to be responsive to ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)]. (…) |

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
CFTR Chloride Transport Assay in Fisher Rat Thyroid (FRT) cells expressing mutant CFTR
In order to evaluate the response of mutant CFTR protein to ivacaftor, total chloride transport was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual CFTR mutations. Ivacaftor increased chloride transport in FRT cells expressing CFTR mutations that result in CFTR protein being delivered to the cell surface. Data shown in Figure 1 are the mean (n=3-7) net change over baseline in CFTR mediated chloride transport following the addition of ivacaftor in FRT cells expressing mutant CFTR proteins. The in vitro CFTR chloride response threshold was designated as a net increase of at least 10% of normal over baseline (dotted line) because it is predictive or reasonably expected to predict clinical benefit. Mutations with an increase in chloride transport of 10% or greater are considered responsive. A patient must have at least one CFTR mutation responsive to ivacaftor to be indicated. Mutations including F508del that are not responsive to ivacaftor potentiation, based on the in vitro CFTR chloride response threshold, are listed in Figure 1 below the dotted line. (see Figure 1)
Note that splice mutations cannot be studied in this FRT assay and are not included in Figure 1. Evidence of clinical efficacy exists for non-canonical splice mutations 2789+5G→A, 3272-53A→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-S7 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 3 weeks of treatment was -49 mmol/L (95% CI -57, -41). The mean changes in sweat chloride for the mutations for which KALYDECO is indicated ranged from -51 to -8, whereas the range for individual subjects with the G970R mutation was -1 to -11 mmol/L. In an open-label clinical trial in 34 patients ages 2 to less than 6 years administered either 50 mg or 75 mg of ivacaftor twice daily (Trial 7), the treatment difference in mean change in sweat chloride from study baseline to the average of Week 4 and Week 6 of treatment for KALYDECO treated patients was -45 mmol/L (95% CI -53, -38) [see Use in Specific Populations (8.4)]. In a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in patients with CF age 12 years and older who were heterozygous for the F508del mutation and with a second CFTR mutation predicted to be responsive to ivacaftor (Trial 6), the mean absolute change from baseline in sweat chloride for patients aged 12 months to less than 24 months (n=10) was -73.5 mmol/L (95% CI -86.0, -61.0) at Week 24, and the mean absolute change from baseline in sweat chloride for patients aged 6 months to less than 12 months (n=6) was -58.6 mmol/L (95% CI -75.9, -41.3) at Week 24. [see Use in Specific Populations (8.4)]. (…) |

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


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13.2 Clinical Trials Experience
The efficacy and safety of KALYDECO in patients with CF who have an R117H mutation in the CFTR gene 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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</table>

#### 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 heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (see Adverse Reactions (6) and Clinical Studies (14)).

The safety and efficacy of SYMDEKO in patients with CF younger than 12 years of age have not been studied.

#### 12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

**Effects on Sweat Chloride**

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

#### 14 CLINICAL STUDIES

**Dose Ranging**

Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF (homozygous for the F508del mutation) 18 years of age and older with a screening ppFEV1 ≥40. In the study, 34 and 106 patients, respectively, received tezacaftor at once-daily doses of 10 mg, 30 mg, 100 mg, or 150 mg alone or in combination with ivacaftor 150 mg q12h, and 33 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean ppFEV1 change from baseline were observed with tezacaftor in combination with ivacaftor. Tezacaftor/ivacaftor in general had a greater mean treatment effect than tezacaftor alone. No additional benefit was observed at tezacaftor doses greater than 100 mg daily.

**Efficacy**

The efficacy of SYMDEKO in patients with CF aged 12 years and older was evaluated in three Phase 3, double-blind, placebo-controlled trials (Trials 1, 2, and 3).

**Trial 1** was a 24-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were homozygous for the F508del mutation in the CFTR gene. Patients were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo.

**Trial 2** was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in CF patients who were heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Mutations predicted to be responsive were selected for the study based on the clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro responsiveness to tezacaftor/ivacaftor (see Clinical Studies (14.2)).

**Trial 3** was a 12-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro testing to tezacaftor and/or ivacaftor. (…)

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

Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean ppFEV1 at baseline was 60.0% (range: 27.8% to 96.2%). (see Table 8 and Figure 2) (…)

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

Trial 2 evaluated 244 patients with CF aged 12 years and older (mean age 34.8 years). The mean ppFEV1 at baseline was 62.3% (range: 34.6 to 93.5). Of the 244 patients included in the efficacy analysis, 146 patients had a splice mutation and 98 patients had a missense mutation as the second allele. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (see Table 9).

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

**14.3 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/ivacaftor (Trial 3)**

Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.3 years) who were heterozygous for the F508del mutation and had a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Patients with the F508del mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, G970R, I507del, R1066C, R347P, 1154insTC, 1811+1G>delG, 2184delA.

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

Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean ppFEV1 at baseline was 60.0% (range: 27.8% to 96.2%). (see Table 8 and Figure 2) (…)

**14.5 Trial in Patients with CF Who Were Homozygous for the F508del Mutation and a Second Mutation Predicted to be Responsive to Tezacaftor/ivacaftor (Trial 3)**

Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.3 years) who were heterozygous for the F508del mutation and had a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Patients with the F508del mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, G970R, I507del, R1066C, R347P, 1154insTC, 1811+1G>delG, 2184delA.

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

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

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Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2020

<table>
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<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Biomarker†</th>
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<td>Ixabepilone (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES Combination Therapy. (…) Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6. (…) Monotherapy HER2-positive patients must also have progressed during or after discontinuation of trastuzumab. In this study, the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian. Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 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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<tr>
<td>022065, 10/18/2011</td>
<td>Ixabepilone (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>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.</td>
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<td>204839, 04/28/2016</td>
<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 3% (…).</td>
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<td>Lansoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.3 Tiacrolimus Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.</td>
</tr>
<tr>
<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 Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TYKERB® is indicated in combination with: • capcitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capcitabine. • letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpress HER2. • capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine.</td>
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<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: TYKERB is indicated in combination with: (…) • luteinase for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. (…)</td>
</tr>
</tbody>
</table>

### 14 CLINICAL STUDIES

#### 14.1 HER2-Positive Metastatic Breast Cancer

The efficacy and safety of TYKERB in combination with capcitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErB2) 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). (…) The second randomized, open-label study compared the safety and efficacy of taxane-based chemotherapy plus TYKERB to taxane-based chemotherapy plus trastuzumab as first-line therapy in women with HER2-positive, metastatic breast cancer (N = 652). (…) 

#### 14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer

The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or 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). Of all patients randomized to treatment, 219 (17%) patients had tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH) 2 or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2-negative and 115 (9%) patients did not have the 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 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 55% 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) 

#### 14.3 Hormone Receptor-Negative, HER2-Positive Metastatic Breast Cancer

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-negative (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. (…) 

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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 (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, rifapentin, phenobarbital, St. John’s wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability.</td>
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</tbody>
</table>
| 022059, 12/06/2018                     | Lapatinib (4) | Oncology | HLA-DRB1 | Clinical Pharmacology | 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 chemotheraphy for their metastatic disease, patients received letrozole with or without TYKERB. (...)  
Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer: In another randomized, Phase 3 clinical trial of postmenopausal patients (N = 355) with hormone receptor positive (HR+), HER2-2 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. (...)  
8 USE IN SPECIFIC POPULATIONS  
8.5 Geriatric Use  
Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capcetabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-2 positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (...)  
14 CLINICAL STUDIES  
14.1 HER2-Positive Metastatic Breast Cancer  
(...) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ERB2 (HER2) 3+ or IHC 2+ with FISH confirmation. (...)  
14.2 Hormone Receptor-Positive, HER2-2 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 1,288 postmenopausal women with hormone receptor (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, HER2-2 positive and HER2-2 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+/HER2-2 positive, metastatic breast cancer, which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies. (...)  |
| 210861, 11/20/2018                     | Larotrectinib | Oncology | NTRK | Indications and Usage, Dosage and Administration | 1 INDICATIONS AND USAGE  
VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:  
• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, (…)  
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 chemotheraphy for their metastatic disease, patients received letrozole with or without TYKERB. (...)  
Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer: In another randomized, Phase 3 clinical trial of postmenopausal patients (N = 355) with hormone receptor positive (HR+), HER2-2 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. (...)  
8 USE IN SPECIFIC POPULATIONS  
8.5 Geriatric Use  
Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capcetabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-2 positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (...)  
14 CLINICAL STUDIES  
14.1 HER2-Positive Metastatic Breast Cancer  
(...) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ERB2 (HER2) 3+ or IHC 2+ with FISH confirmation. (...)  
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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, HER2-2 positive and HER2-2 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+/HER2-2 positive, metastatic breast cancer, which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies. (...)  |

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<td>IFNL3 (IL28B)</td>
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<td>(…) Homogeneous 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; 76% 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>(…) Homogeneous 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); 76% 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>(…) Homogeneous 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 28 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></td>
<td>Previously-Treated Adults with Cirrhosis — SIRIUS (Study 0121)</td>
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<td>(…) Homogeneous 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; 87% 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 54 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/G 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% (26/1357) in non-Black subjects. (…)</td>
</tr>
</tbody>
</table>

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<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
</tr>
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<tbody>
<tr>
<td>206947, 02/20/2020</td>
<td>Lenvatinib</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
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<td></td>
<td>1.2 Myelodysplastic Syndromes</td>
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<td>REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.</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>Myelodysplastic Syndromes</td>
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<td>A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 8 summarizes the adverse events that were reported in ≥5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 9 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient’s underlying disease. (See Tables 9 and 10)</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.5 Geriatric Use</td>
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<td>(…) Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. (…)</td>
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<td></td>
<td>14 CLINICAL STUDIES</td>
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<td>14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality</td>
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<td>The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1-risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. (…)</td>
</tr>
<tr>
<td>207988, 12/22/2015</td>
<td>Lesinurad</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
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<td>7.1 CYP2C9 Inhibitors, CY2P2C9 Poor Metabolizers, and CY2P2C9 Inducers</td>
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<td>Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone), and in CYP2C9 poor metabolizers [see Clinical Pharmacology (12.3)]. (…)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
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<td>12.3 Pharmacokinetics</td>
</tr>
</tbody>
</table>

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|----------------------------------------|-----------------------|-------------------|-------------|-------------------|-----------------|
| 020726, 04/05/2018                     | Lidocaine and Prilocaine (1) | Anesthesiology    | Non-specific (Congenital Methemoglobinemia) | Warnings and Precautions | 5.1 Methemoglobinemia

**INDICATIONS AND USAGE**

1.1 Adjuvant Treatment of Early Breast Cancer

Femara (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

1.3 First and Second-Line Treatment of Advanced Breast Cancer

Femara is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy [see Clinical Studies (14.4, 14.5)].

6 ADVERSE REACTIONS

6.1 Adjuvant Treatment of Early Breast Cancer

(…)

6.1.1 Bone Study

Results of a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) (P<0.0001). (…)

6.1.2 Lipid Study

In a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen. (…)

14 CLINICAL STUDIES

14.1 Updated Adjuvant Treatment of Early Breast Cancer

In a multicenter study enrolling over 8,000 postmenopausal women with resected, receptor-positive early breast cancer, one of the following treatments was randomized in a double-blind manner (See Table 6): (…)

14.2 Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months

A double-blind, randomized, placebo-controlled trial of Femara was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease-free after 6 years of adjuvant treatment with tamoxifen. (See Table 8) (…)

14.3 First and Second-Line Treatment of Advanced Breast Cancer

Femara is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy [see Clinical Studies (14.4, 14.5)].

14.4 First-Line Treatment of Advanced Breast Cancer

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

14.5 Second-Line Treatment of Advanced Breast Cancer

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

| 021451, 11/02/2018 | Lidocaine and Prilocaine (2) | Anesthesiology | G6PD | Warnings and Precautions | 5.1 Methemoglobinemia

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. (…)

1D.3 Pharmacokinetics

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<td>02/1623, 11/02/2018</td>
<td>Lidocaine and Tetracaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia. Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. Local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<tr>
<td>02/1623, 11/02/2018</td>
<td>Lidocaine and Tetracaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia. Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. 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>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>
<tr>
<td>210868, 05/29/2020</td>
<td>Lorlatinib (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE LORBRENA® is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on • crizotinib and at least one other ALK inhibitor for metastatic disease; or • alectinib as the first ALK inhibitor therapy for metastatic disease; or • ceritinib as the first ALK inhibitor therapy for metastatic disease. This indication is approved under accelerated approval based on tumor 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.</td>
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<tr>
<td>210868, 05/29/2020</td>
<td>Lorlatinib (2)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience</td>
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</tr>
</thead>
</table>
| Luspatercept-aamt | Hematology | HBB | Clinical Studies | 14 CLINICAL STUDIES 14.1 Beta Thalassemia

(….) The BELIEVE trial excluded patients with hemoglobin S/β-thalassemia or alpha-thalassemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of ESA, immunosuppressant, or hydroxyurea therapy were also excluded. The median age was 30 years (range: 18-66). The trial was comprised of patients who were 42% male, 54.2% white, 34.8% Asian, and 6.3% Black or African American. The percent of patients reporting their race as “other” was 7.7% and race was not collected or reported for 3% of patients. Table 4 summarizes the baseline disease-related characteristics in the BELIEVE study. (See Table 4) (…) |

| Lusutrombopag (1) | Hematology | F2 (Prothrombin) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

(…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |

| Lusutrombopag (2) | Hematology | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

(…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |

| Lusutrombopag (3) | Hematology | PROC | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

(…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |

| Lusutrombopag (4) | Hematology | PROS1 | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

(…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |

| Lusutrombopag (5) | Hematology | SERPINC1 (Antithrombin III) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

(…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |

| Lutetium Dotatate Lu-177 | Oncology | SSTR | Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE

LUTATHERA is indicated for the treatment of somatostatin receptor-positive gastrinomenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. |

| 208700, 05/29/2020 | 208700 | Oncology | 6 ADVERSE REACTIONS

1. Clinical Trials Experience

The data in Warnings and Precautions reflect exposure to LUTATHERA in 111 patients with advanced, progressive midgut neuroendocrine tumors (NETTER-1). Safety data in Warnings and Precautions were also obtained in an additional 22 patients in a non-randomized pharmacokinetic substudy of NETTER-1 and in a subset of patients (811 of 1214) with advanced somatostatin receptor-positive tumors enrolled in ERASMUS (see Warnings and Precautions (5)) (…) NETTER-1

The safety data of LUTATHERA with octreotide was evaluated in NETTER-1 (see Clinical Studies (14.1) Patients with progressive, somatostatin receptor-positive midgut carcinoid tumors to receive LUTATHERA 7.4 GBq (200 mCi) administered every 8 to 16 weeks concurrently with the recommended amino acid solution and with long-acting octreotide (30 mg administered by intramuscular injection within 24 hours of each LUTATHERA dose) (n = 111), or high-dose octreotide (defined as long-acting octreotide 60 mg by intramuscular injection every 4 weeks (n = 112) (see Clinical Studies (14.1) (…) ERASMUS

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<tbody>
<tr>
<td>019823, 06/05/1998</td>
<td>Mafenide</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>WARNINGS: Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate. ADVERSE REACTIONS: (…) Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate.</td>
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<tr>
<td>010721, 06/28/2019</td>
<td>Meclizine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions</td>
<td>8 USE IN SPECIFIC POPULATIONS: 8.8 Genetic CYP2D6 Polymorphism: The genetic polymorphism of CYP2D6 that results in poor-, intermediate-, extensive-, and ultrarapid metabolizer phenotypes could contribute to large inter-individual variability in meclizine exposure. Therefore, when ANTIVERT® is administered to patients with CYP2D6 polymorphism, monitor for adverse reactions and clinical effect accordingly.</td>
</tr>
<tr>
<td>211210, 10/19/2019</td>
<td>Meloxicam</td>
<td>Anesthesiology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS: 8.8 Poor Metabolizers of CYP2C9 Substrates: In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin or phenytoin), consider dose reduction, as these patients may have abnormally high plasma levels of meloxicam due to reduced metabolic clearance. Monitor these patients for adverse effects.</td>
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<td>012220, 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>012250, 11/02/2018</td>
<td>Mepivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital/Hereditary Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…</td>
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<tr>
<td>205919, 04/29/2020</td>
<td>Mercaptopurine (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings and Precautions, Clinical Pharmacology</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/m2) as a single daily dose. After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cellularity. Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression. 2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]. Homozygous deficiency in either TPMT or NUDT15 Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Heterozygous deficiency in TPMT and/or NUDT15 Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. 5 WARNINGS AND PRECAUTIONS 5.1 Myelosuppression The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia. Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN (see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)). Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by 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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<tr>
<td>205919, 04/29/2020</td>
<td>Mercaptopurine (2)</td>
<td>Oncology</td>
<td>NUDT15</td>
<td>Dosage and Administration, Warnings and Precautions, Clinical Pharmacology</td>
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| 204630, 05/21/2018                   | Methylene Blue | Hematology | G6PD | Contraindications, Warnings and Precautions | Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]. Homozygous deficiency in either TPMT or NUDT15 Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Heterozygous deficiency in TPMT and/or NUDT15 Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. 4 CONTRAINDICATIONS PROVAYBLUE™ is contraindicated in the following conditions: • Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)]. • Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia [see Warnings and Precautions (5.3, 5.4)]. 5 WARNINGS AND PRECAUTIONS 5.3 Lack of Effectiveness Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to any amines such as aniline or sulfia drugs such as dapsone. Monitor response to therapy with PROVAYBLUE™ through resolution of methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a response, consider additional treatment options [see Dosage and Administration (2.2)]. Patients with glucose-6-phosphate dehydrogenase deficiency may not reduce PROVAYBLUE™ to its active form in vivo. PROVAYBLUE™ may not be effective in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency. 5.4 Hemolytic Anemia Hemolysis can occur during treatment of methemoglobinemia with PROVAYBLUE™. Laboratory testing may show Heinz bodies, elevated indirect bilirubin and low haptoglobin, but the Coombs test is negative. The onset of anemia may be delayed 1 or more days after treatment with PROVAYBLUE™. The anemia may require red blood cell transfusions. [see Adverse Reactions (6.1)]. Use the lowest effective number of doses of PROVAYBLUE™ to treat methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a response, consider additional treatment options. PROVAYBLUE™ is contraindicated for use in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency [see Contraindications (4)]. 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. TPMT15 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 TPMT15 gene, and approximately 21% have one loss-of-function allele. The r.P119C 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 phototachy 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)].
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| 017854, 08/29/2017                     | Metoclopramide (1) | Gastroenterology | CYB5R      | Use in Specific Populations | 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 (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)]. |
| 017854, 08/29/2017                     | Metoclopramide (2) | Gastroenterology | G6PD       | Use in Specific Populations, Overdosage | 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 (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)]. |
| 017854, 08/29/2017                     | Metoclopramide (3) | Gastroenterology | CYP2D6     | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 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 Gastroparesis  
The recommended adult dosage for the treatment of acute and recurrent diabetic gastroparesis is 10 mg four times daily for 2 to 8 weeks, depending on symptomatic response. Avoid Reglan treatment for greater than 12 weeks [see Warnings and Precautions (5.1)]. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 40 mg. Table 2 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 2)  
8 USE IN SPECIFIC POPULATIONS  
8.9 CYP2D6 Poor Metabolizers  
Metoclopramide is a substrate of CYP2D6. The elimination of metoclopramide may be slowed in patients who are CYP2D6 poor metabolizers (compared to patients who are CYP2D6 intermediate, extensive, or ultra-rapid metabolizers); possibly increasing the risk of dystonic and other adverse reactions to Reglan [see Clinical Pharmacology (12.3)]. Reduce the Reglan dosage in patients who are poor CYP2D6 metabolizers [see Dosage and Administration (2.2, 2.3)]. |
| 019962, 05/06/2014                     | Metoprolol | Cardiology       | CYP2D6     | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS  
7.2 CYP2D6 Inhibitors  
Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propranolol 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 propranolol 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: Metoprolol undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monodeethylmetoprolol, 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)]. |
| 207997, 03/04/2020                      | Midostaurin (1) | Oncology         | FLT3       | Indications and Usage, Dosage | 1 INDICATIONS AND USAGE  
1.1 Acute Myeloid Leukemia  
Midostaurin is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol’s cardiodepressant effect [see Drug Interactions (7.2)]. |

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<td>In an in vitro assay (HEK-293 assay), Human Embryonic Kidney (HEK-293) cell lines were transfected with specific GLA variants (mutations) which produced mutant alpha-Gal A proteins. In the transfected cells, amenable of the GLA variants was assessed after a 5-day incubation with 10 micromol/L migalastat. A GLA variant was categorized as amenable if the resultant mutant alpha-Gal A activity (measured in the cell lysates) met two criteria: 1) it showed a relative increase of at least 20% compared to the pre-treatment alpha-Gal A activity, and 2) it showed an absolute increase of at least 3% of the wild-type (normal) alpha-Gal A activity. The in vitro assay did not evaluate trafficking of the mutant alpha-Gal A proteins into the lysosome or the dissociation of migalastat from the mutant alpha-Gal A proteins within the lysosome. Also, the in vitro assay did not test whether a GLA variant causes Fabry disease or not. The GLA variants which are amenable to treatment with GALAFOLD, based on the in vitro assay data, are shown in Table 2. Inclusion of GLA variants in this table does not reflect interpretation of their clinical significance in Fabry disease. Whether a certain amenable GLA variant in a patient with Fabry disease is disease-causing or not should be determined by the prescribing physician (in consultation with a clinical genetics professional, if needed) prior to treatment initiation. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease). (See Table 2) If a GLA variant does not appear in Table 2, it is either non-amenable (if tested) or has not been tested for in vitro amenability. For further information, please contact Amicus Medical Information at 1-877-4AMICUS or <a href="mailto:medinfo@amicus.com">medinfo@amicus.com</a>.</td>
<td>CYP2D6</td>
<td>Urology</td>
<td>Mirabegron</td>
<td>Clinical Pharmacology</td>
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<td>Reduced Plasma Cholinesterase Activity</td>
<td>O20098, 07/26/2018</td>
<td>Anesthesiology</td>
<td>Mivacurium</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
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<td>Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiophate, and certain antiinflammatory drugs). MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.1 to 0.2 mg/kg MIVACRON, the clinically effective duration of action was 8 minutes to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients. As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (one in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED10-20 in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.</td>
<td>BCHE</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
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<td>Transplantation</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>021742, 11/30/2017</td>
<td>Nebivolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
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Pharmacodynamics
Administration of MIVACRON over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of MIVACRON may be prolonged in patients with reduced plasma cholinesterase activity (see PRECAUTIONS - Reduced Plasma Cholinesterase Activity and CLINICAL PHARMACOLOGY - Individualization of Dosages subsection).
Individualization of Dosages
Reduced Plasma Cholinesterase Activity
The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produce 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).

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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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<tr>
<td>076037, 07/17/2014</td>
<td>Nefazodone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Cardiovascular-Active Drugs Digoxin When nefazodone (200 mg BID) and digoxin (0.2 mg QD) 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 triclopropanol 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 isozyme 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, desmethylmorphinan, 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 not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme.</td>
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<td>208051, 02/25/2020</td>
<td>Neratinib (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 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 capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior HER2-based regimens [see Clinical Studies (14.2)]. 6 ADVERSE REACTIONS 6.1 Clinical Trials ExperienceExtended Adjuvant Treatment of Early Stage Breast Cancer ExteNET The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. (...) Advanced or Metastatic Breast Cancer NALA The data described below reflect the safety data of NERLYNX plus capecitabine in NALA, a randomized, multicenter, multinational, open-label, active-controlled study of HER2+ metastatic breast cancer in patients, with or without brain metastases, who have received two or more prior anti-HER2-based regimens in the metastatic setting. (...) 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 (NCT00879709), 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 NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab in women with HER2-positive breast cancer. The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX in combination with capecitabine was studied in NALA (NCT1908573), a randomized, multicenter, open-label clinical trial in patients (N=521) 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 immunostaining score (IHC) score of 3+ or IHC 2+ with confirmatory in situ hybridization (ISH) positive. Fifty-nine percent of these patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). 69% had received two 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-viscerocentric disease. Patients with asymptomatic or stable brain metastases were included in NALA trial (16%). (...) 14.1 Extended Adjuvant Treatment of Early Stage Breast Cancer (...), and without an additional anti-diarrheal treatment. 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. 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Fifty-nine percent of these patients were hormone receptor positive (HR+) and 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-viscerocentric disease. Patients with asymptomatic or stable brain metastases were included in NALA trial (16%). (...) 14.2 Advanced or Metastatic Breast Cancer NERLYNX in combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. NERLYNX in combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. 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## Table of Pharmacogenomic Biomarkers in Drug Labeling
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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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<th>Biomarker</th>
<th>Labeling Sections</th>
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<tbody>
<tr>
<td>022068, 09/25/2019</td>
<td>Nilotinib (1)</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>the following factors: hormone receptor status, nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. (...) Fifty-seven percent (57%) had hormone receptor positive disease (defined as ER-positive and/or PR-positive). 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. (See Table 12) (...) HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment. HER2 positivity was defined as a HER2 immunohistochemistry (IHC) score of 3+ or IHC 2+ with confirmatory in situ hybridization (ISH) positive. Fifty-nine percent of these patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-); 69% had received two prior anti-HER2 based regimens, 31% had received three or more prior anti-HER2 based regimens, 81% had visceral disease, and 19% had non-visceral only disease. Patients with asymptomatic or stable brain metastases were included in NALA trial (16%). (See Table 14) (...)</td>
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### Notes:
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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.
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Upon the loss of MR4.0 (corresponding to BCR-ABL ≤ 0.1%IS) during the treatment-free phase, monitor BCR-ABL transcript levels every 2 weeks until BCR-ABL levels remain lower than major molecular response (MMR, corresponding to MR3.0 or BCR-ABL ≤ 0.1%IS) for 4 consecutive measurements. The patient can then proceed to the original monitoring schedule.

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

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- **Therapeutic areas do not necessarily reflect the CDER review division.**
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  1. Adult patients with newly diagnosed Ph+ CML-CP 60 month analysis and.
  2. Adult patients with resistant or intolerant Ph+ CML-CP or imatinib resistant or intolerant Ph+ CML-CP treated at the recommended dose of 330 mg/m² twice daily (n=69) [see Clinical Studies (14.5)]. The median time on treatment with Tasigna was 13.8 months (range: 0.7 to 30.9 months). The median actual dose intensity was 435.5 mg/m²/day (range: 149 to 517 mg/m²/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%.
- **In Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP**: The data below reflect exposure to Tasigna from two studies in pediatric patients from 2 to less than 18 years of age with either newly diagnosed Ph+ CML-CP or imatinib resistant or intolerant Ph+ CML-CP treated at the recommended dose of 330 mg/m² twice daily (n=69) [see Clinical Studies (14.5)]. The median time on treatment with Tasigna was 13.8 months (range: 0.7 to 30.9 months). The median actual dose intensity was 435.5 mg/m²/day (range: 149 to 517 mg/m²/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%.
- **Growth Retardation in Pediatric Population**: In a multicenter, open-label, single-arm study of 58 pediatric patients with newly diagnosed or resistant Ph+ CML-CP treated with Tasigna, with a median exposure of 33 months in each cohort, adverse reactions associated with growth and deceleration of growth in regard to height were reported in 3 patients (5%). The adverse reactions include growth retardation in 2 adolescent patients and growth hormone deficiency with body height below normal in the remaining patient (age category: child). Of the 58 pediatric patients, 12.1% (n = 7) experienced a decrease of two main height percentiles compared with baseline (percentile lines: 5th, 10th, 25th, 50th, 75th, 95th, and 95th). Close monitoring of growth in pediatric patients under Tasigna treatment is recommended [see Warnings and Precautions (5.14)].

**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 no data for pediatric patients under 2 years of age. Use of Tasigna in pediatric patients 1 to less than 2 years of age is supported by efficacy in pediatric patients 2 to 6 years of age.
  - Use of Tasigna in pediatric patients 1 to less than 18 years of age is supported by evidence from two clinical trials [see Clinical Studies (14.5)]. The 25 patients with newly diagnosed Ph+ CML 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**

- **12.3 Pharmacokinetics**: 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 Cmax was comparable across all age groups (pediatric patients from ages 2 to less than 18 years), diseases (patients with newly diagnosed and resistant or intolerant Ph+ CML) and studies.

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

**14 CLINICAL STUDIES**

- **14.1 Adult Newly Diagnosed Ph+ CML-CP**: The ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Newly Diagnosed patients) study (NCT00471497) was an open-label, multicenter, randomized trial conducted to determine the efficacy of Tasigna versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. Efficacy was based on a total of 846 patients: 283 patients in the imatinib 400 mg once daily group, 282 patients in the Tasigna 300 mg twice daily group, 281 patients in the Tasigna 400 mg twice daily group (…)

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<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics</td>
</tr>
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</table>

The primary efficacy endpoint was major molecular response (MMR) at 12 months after the start of study medication. MMR was defined as less than or equal to 0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a greater than or equal to 3 log reduction of BCR-ABL transcript from standardized baseline. Efficacy endpoints are summarized in Table 12. (See Table 12) 

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

Study CAMIN107A2101 (referred to as Study K2101) (NCT01009701) 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-CP and 137 patients with CML-AP with a minimum follow-up of 24 months were enrolled. In this study, about 50% of CML-CP and CML-AP patients were males, over 90% (CML-CP) and 80% (CML-AP) were Caucasian, and approximately 30% were age 65 years or older.

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

The ENESTremendom (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 MolecularAID MRD™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 190 patients (88.4%) entered the “Treatment-free Remission” (TFR) phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

- The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS)
- No more than two assessments falling between MR4 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤ 0.01% IS)
- The median age of patients who entered the TFR phase was 55 years, 49.5% were females, and 21.1% of the patients were ≥ 65 years of age. BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0.

Biweekly monitoring ended at one of the following time points:

- Loss of MMR requiring patient to 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 Nilotinib therapy**

The ENESTtop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Stopt) study (NCT01688905) is an open-label, multicenter, single-arm study, where 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥ 3 years (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 MolecularAID MRD™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 156 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 less than or equal to 0.01% IS were considered having a confirmed loss of MR4.0, requiring reinitiation of Tasigna treatment. Patients with loss of MMR in the TFR phase immediately restarted Tasigna treatment without conformation. All patients who restarted Tasigna therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks.

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

The safety and efficacy of Tasigna in pediatric patients with Ph+ CML-CP have been investigated in two studies: Study CAMIN107A2120 (NCT01177544), 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 CAMIN107A2203 (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 460 mg). Data were pooled from a total of 69 pediatric patients (from 2 to less than 18 years of age) with either newly diagnosed Ph+ CML-CP (n=25; 6 children from 2 to less than 12 years and 19 adolescents from 12 to less than 18 years) or imatinib/dasatinib resistant or intolerant Ph+ CML-CP (n=44; 18 children from 2 to less than 12 years and 26 adolescents from 12 to less than 18 years).

In patients with resistant or intolerant CML, the major molecular response (MMR; BCR-ABL/ABL ≤ 0.0032% IS) during 1 year.

- The median time on treatment with Tasigna was 13.90 months (range: 0.7 to 30.9 months).

In patients with resistant or intolerant CML, the major molecular response (MMR; BCR-ABL/ABL ≤ 0.01% IS) was 40.9% (18/44; 95% CI: 26.3%; 56.8%) at 12 cycles (28 days per cycle).

In patients with newly diagnosed CML, the MMR rate was 60.0% (15/25; 95% CI: 38.7%; 78.9%) at 12 cycles. In patients with resistant or intolerant CML, the cumulative MMR rate was 64.0% (16/25) by cycle 12.

Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, the median time to first MMR was 2.8 months (range: 0.0 to 11.3). For the 17 patients with newly diagnosed CML who achieved MMR, the median time to first MMR was 5.6 months (range: 2.7 to 16.6).

Among patients with resistant or intolerant CML, 4.5% of patients achieved BCR-ABL/ABL ≤ 0.0032% IS (MR4.5) by the cut-off date. Among patients with newly diagnosed CML, the percentage of patients who achieved MR4.5 was 28.0%. (See Table 13)
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<td>Nitrofurantoin</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td><strong>WARNINGS</strong>&lt;br&gt;Hemolytic anemia&lt;br&gt;Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn. <strong>ADVERSE REACTIONS</strong>&lt;br&gt;Laboratory Adverse Events&lt;br&gt;The following laboratory adverse events have been reported with the use of nitrofurantoin; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see Warnings), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.</td>
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<td>BRAF</td>
<td>Adverse Reactions, Clinical Studies</td>
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### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

**Previously Treated Metastatic Melanoma**

(…)

**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**

(…)

**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). (…)

**CHECKMATE-141**

(…) 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 (48%); 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%). (…)

#### 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 and TB greater than 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).

### Footnotes

* 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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<tr>
<th>Date</th>
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<th>NDA Number, BLA</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
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<th>Labeling Sections</th>
<th>Labeling Text</th>
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<td>14.1 Unresectable or Metastatic Melanoma</td>
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<td>(…) 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). (…)</td>
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<td>(…) Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma 44 Reference ID: 4158384 (11%), elevated LDH level (37%), PD-L1 greater than or equal to 5% tumor cell membrane expression (35%), and history of brain metastasis (4%). (…)</td>
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<td>(…) Randomization was stratified by PD-L1 expression (≥5% vs. &lt;5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). (…)</td>
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<td>(…) 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 50% tumor cell membrane expression as determined by the clinical trial assay (46%); and prior adjuvant therapy (22%). (…)</td>
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<td>14.2 Adjuvant Treatment of Melanoma</td>
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<td>14.3 Metastatic Non-Small Cell Lung Cancer (NSCLC)</td>
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<td>First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC): Expressing PD-L1 (≥1%): In Combination with Ipilimumab</td>
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<td>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. (…)</td>
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<td>(…) 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). (…)</td>
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<td>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 16% 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. (…)</td>
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<td>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. (…)</td>
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<td>CHECKMATE-06A (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 [IAACS]), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. (…)</td>
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<td>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. Patients were enrolled regardless of their tumor PD-L1 status. (…)</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2020

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<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| **Previously Untreated Renal Cell Carcinoma**

**Previous Treated Renal Cell Carcinoma**

**14.4 Small Cell Lung Cancer**

**CHECKMATE-032** (NCT01829394) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic small tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinum-based chemotherapy to receive treatment with OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. (…)

**14.5 Advanced Renal Cell Carcinoma**

**Previously Treated Renal Cell Carcinoma**

**CHECKMATE-025** (NCT01688784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior antiangiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) >70% and patients were included regardless of their PD-L1 status. (…)

**14.6 Classical Hodgkin Lymphoma**

**14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck**

**CHECKMATE-141** (…)

**14.8 Urothelial Carcinoma**

**CHECKMATE-275** (…)

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**Last Updated: 06/2020**

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<tr>
<td>125554, 06/10/2020</td>
<td>Nivolumab</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>INDICATIONS AND USAGE</td>
<td><strong>1.9 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer</strong>&lt;br&gt;OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years old and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.9)]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
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</table>

**OPDIVO is indicated for the treatment of 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.**<br>OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. **OPDIVO is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.**

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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.
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| 125554, 06/10/2020                     | Nivolumab (5) | Oncology         | ALK        | Indications and Usage, Adverse Reactions, Clinical Studies | First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab  
The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.3)]. (…)

14 CLINICAL STUDIES
14.3 Metastatic Non-Small Cell Lung Cancer
First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Ipilimumab  
CHECKMATE-227 (NCT02477926) 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 Ipilimumab and Platinum-Doubltet Chemotherapy  
CHECKMATE-6LA (NCT0215706) 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. (…)

Second-line Treatment of Metastatic Non-Squamous NSCLC  
(…) CHECKMATE-057 (NCT01673887) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum 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 66 years (range: 18 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (65%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%). 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. (…)

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.  
• OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.  
• OPDIVO is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

6 ADVERSE REACTIONS
Metastatic Non-Small Cell Lung Cancer  
First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab  
The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.3)]. (…)

14 CLINICAL STUDIES
14.3 Metastatic Non-Small Cell Lung Cancer
First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Ipilimumab  
CHECKMATE-227 (NCT02477926) 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 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. (…)

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doubltet Chemotherapy  
CHECKMATE-6LA (NCT0215706) 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. (…)

Second-line Treatment of Metastatic Non-Squamous NSCLC

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<td>018013, 04/09/2010</td>
<td>Nortriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Drugs Metabolized by P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).</td>
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<tr>
<td>209531, 10/10/2018</td>
<td>Nusinersen</td>
<td>Neurology</td>
<td>SMN2</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMAOCOLOGY 12.2 Pharmacoodynamics 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>125486, 03/27/2020</td>
<td>Obinutuzumab</td>
<td>Oncology</td>
<td>MSI4A1 (CD20 antigen)</td>
<td>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 existing medical conditions or reduced renal function as measured by creatinine clearance (CrCl) &lt; 70 mL/min. (...)</td>
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<tr>
<td>208530, 05/05/2010</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>1 INDICATIONS AND USAGE 1.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. 1.4 Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. 1.5 Germine BRCA-mutated HER2-negative Metastatic Breast Cancer Lynparza is indicated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. 1.6 First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].</td>
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- Reassessed Ovarian Cancer, Germline BRCAm Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration/Resistant Prostate Cancer
- Maintenance treatment until disease progression or unacceptable toxicity for:
  - Maintenance treatment of recurrent ovarian cancer
  - Advanced germline BRCA-mutated ovarian cancer
  - Germline BRCA-mutated HER2-negative metastatic breast cancer
  - First-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma.

5 WARNINGS AND PRECAUTIONS
5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia
In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent [see Adverse Reactions (6.1)], the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was (...) 6 ADVERSE REACTIONS
First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer
SOLO-1
The safety of Lynparza for the maintenance treatment of patients with BRCA-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1, a placebo-controlled, double-blind study in which 390 patients received either Lynparza 300 mg BID (n=260) or placebo tablets (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo. (...) Maintenance Treatment of Recurrent Ovarian Cancer
SOLO-2
The safety of Lynparza for the maintenance treatment of patients with platinum sensitive gBRCAm ovarian cancer was investigated in SOLO-2. This study was a placebo-controlled, double-blind study in which 294 patients received either Lynparza 300 mg (2 x 150 mg tablets) twice daily (n=195) or placebo tablets twice daily (n=99) until disease progression or unacceptable toxicity. (…)

Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy Pooled data
The safety of Lynparza was investigated in 223 patients (pooled from 6 studies) with gBRCAm advanced ovarian cancer who had received 3 or more prior lines of chemotherapy [see Clinical Studies (14.4)]. Patients received Lynparza capsules 450 mg orally twice daily until disease progression or unacceptable tolerability. The median exposure to Lynparza in these patients was 5.2 months. (...) Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
OlympiAD
The safety of Lynparza was evaluated in gBRCAm patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD [see Clinical Studies (14.5)]. (...) First-line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma
POLO
The safety of Lynparza as maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma following first-line treatment with platinum-based chemotherapy was evaluated in POLO [see Clinical Studies (14.6)]. (...) 14 CLINICAL STUDIES
14.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer
The efficacy of Lynparza was evaluated in SOLO-1 (NCT01844986), a randomized (2:1), double-blind, placebo-controlled, multicenter trial in patients with BRCA-mutated advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy. (...)
A total of 391 patients were randomized, 260 to Lynparza and 131 to placebo. The median age of patients treated with Lynparza was 53 years (range: 29 to 82) and 53 years (range: 31 to 84) among patients on placebo. The ECOG performance status (PS) was 0 in 77% of patients receiving Lynparza and 80% of patients receiving placebo. Of all patients, 82% were White, 36% were enrolled in the U.S. or Canada, and 82% were in complete response to their most recent platinum-based regimen. The majority of patients (n=389) had germline BRCA mutation (gBRCAm), and 2 patients had somatic BRCAm (sBRCAm). Of the 391 patients randomized in SOLO-1, 386 were retrospectively or prospectively tested with a Myriad BRACAnalysis test and 383 patients were confirmed to have deleterious or suspected deleterious gBRCAm status; 253 were randomized to the Lynparza arm and 130 to the placebo arm. Two out of 391 patients randomized in SOLO-1 were confirmed to have sBRCAm based on an investigational Foundation Medicine tissue test. (...)
14.3 Maintenance Treatment of Recurrent Ovarian Cancer
The efficacy of Lynparza was investigated in two randomized, placebo-controlled, double-blind, multicenter studies in patients with recurrent ovarian cancers who were in response to platinum-based therapy. SOLO-2
The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874353), a randomized (2:1) double-blind, placebo-controlled trial in patients with gBRCAm ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomized to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. (...) All patients had a deleterious or suspected deleterious germline BRCA mutation as detected either by a local test (n=236) or central Myriad CLIA test (n=59), subsequently confirmed by BRACAnalysis CDx® (n=286). (...) |

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<td>208508, 05/19/2020</td>
<td>Olaparib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>A retrospective analysis for germline BRCA mutation status, some performed using the Myriad test, indicated that 36% (n=36) of patients from the ITT population had deleterious gBRCA mutation, including 39% (n=363) of patients on Lynparza and 33% (n=343) of patients on placebo. (…)</td>
</tr>
</tbody>
</table>

1 **INDICATIONS AND USAGE**

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

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].

2 **DOSAGE AND ADMINISTRATION**

2.1 **Patient Selection**

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics. Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HR gene mutations, including BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

2.2 **Recommended Dosing**

Recurrent Ovarian Cancer, Germline BRCA-mutated Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and 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 HER2-negative metastatic breast cancer
- First-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma
- HRR gene-mutated metastatic castration-resistant prostate cancer

Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchectomy.

6 **ADVERSE REACTIONS**

Treatment of gBRCAm HER2-negative Metastatic Breast Cancer

OlympiAD

The safety of Lynparza tablets as monotherapy was also evaluated in gBRCAm patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD. (…)

14 **CLINICAL STUDIES**

14.5 **Treatment of Germline BRCA-mutated HER2-negative Metastatic Breast Cancer**

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. (…)
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</table>
| 208558, 05/19/2020                    | Olaparib (3) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.5 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious BRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. |

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| 208558, 05/19/2020                    | Olaparib (4) | Oncology | BRCA, Genomic Instability (Homologous Recombination Deficiency) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab
Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. |

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<td>Oncology</td>
<td>Homologous Recombination Repair</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>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)]. (…)</td>
</tr>
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**14 CLINICAL STUDIES**

**14.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab**

PAOLA-1 (NCT02477644) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomization was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and IBCRM 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) (…) |

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

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].

**6 ADVERSE REACTIONS**

### 6.1 Clinical Trial Experience

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer (PROfound)

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

**14 CLINICAL STUDIES**

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

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), 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 HRR gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized to Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (BARD1, BRI1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) were randomized to Cohort B; patients with mutations (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. (…) |

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<td>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 (BARF1, BRIP1, CDXK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD52L4) were randomized in Cohort B; patients with mutations (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, Lanoxin 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 HRR mutations for patients in the Lynparza arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an ATM mutation alone and 2 patients with co-occurring mutations (one with PALB2+PPP2R2A and one with CDK12+PALB2). (See Table 27) (…)</td>
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<td>The efficacy of LARTRUVUO was demonstrated in Trial 1, an open-label, randomized, active-controlled study. Eligible patients were required to have soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy, a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate but had not been administered. ECOG PS of 0-2, and tumor specimen available for assessment of PDGFRA expression by an investigational use assay. Patients were randomized (1:1) to receive LARTRUVUO in combination with doxorubicin or doxorubicin as a single agent. PDGFRA expression (positive versus negative), number of previous lines of treatment (0 versus 1 or more), histological tumor type (leiomysarcoma versus synovial sarcoma versus all others), and ECOG PS (0 or 1 versus 2) were used to allocate patients in the randomization. (…)</td>
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<td>The efficacy of SYNRIBO was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+] (whether lost or never achieved); or no major cytogenetic response (MCRy) by 52 weeks (i.e., ≥35% Ph+) (whether lost or never achieved); or progressive leukocytosis. (See Table 5)</td>
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<td>207931, 07/23/2018</td>
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<td>14.2 Clinical Trial Results in Adults with Chronic GT4 HCV Infection without Cirrhosis (…) Of 59 GT4-infected subjects had a median age of 51 years (range: 49 to 70); 64% were treatment-naive, 17% were prior pegIFN/RBV null responders; 7% were prior pegIFN/RBV partial responders, 13% were prior pegIFN/RBV relapsers; 65% were male; 9% were Black; 14% had a body mass index at least 30 kg/m²; 70% had baseline HCV RNA levels at least 800,000 IU/mL; 79% had IL28B (rs1298780) non-CC genotype; 7% had bridging fibrosis (F3); (…) 14.3 Clinical Trial Results in Adults with Chronic GT4 HCV Infection with Compensated Cirrhosis (…) Of the 59 subjects in the 12 week arm, median age was 56 years (range: 43 to 81); 51% were treatment-naive, 29% were prior pegIFN/RBV null responders; 6% were prior pegIFN/RBV partial responders, 12% were prior pegIFN/RBV relapsers; 6% were male; 7% were Black; 17% had a body mass index of at least 30 kg/m²; 76% had baseline HCV RNA levels of at least 800,000 IU/mL; 86% had IL28B (rs1298780) non-CC genotype; 12% had platelet counts less than 90 x 109 per L; and 5% had albumin less than 3.5 mg per dl. (…)</td>
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<tr>
<td>022058, 08/21/2018</td>
<td>Omeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
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<td>Tacrolimus Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3)</td>
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<td>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>12.3 Pharmacokinetics Metabolism</td>
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<tr>
<td>208065, 05/23/2020</td>
<td>Osimertinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>1 INDICATIONS AND USAGE</td>
<td>TAGRISSO 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 mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)].</td>
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<td>Ospemifene</td>
<td>Gynecology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Drug Interactions Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug</td>
</tr>
<tr>
<td>203505, 01/25/2019</td>
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<tr>
<td>202810, 12/13/2018</td>
<td>Oxcarbazepine</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings and Precautions</td>
<td>5.4 Serious Dermatological Reactions Association with HLA-B<em>1502 Patients carrying the HLA-B</em>1502 allele may be at increased risk for SJS/TEN with Oxtellar XR treatment. 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 oxcarbazepine and Oxtellar XR are similar to that of carbamazepine. Available clinical evidence, and data from nonclinical studies showing a direct interaction between immediate release oxcarbazepine and HLA-B</em>1502 protein, suggest that the HLAB<em>1502 allele may also increase the risk for SJS/TEN with Oxtellar XR. The frequency of HLAB</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 Malayasian 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, indigenous peoples of the Americas, Hispanic populations, 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>
</tr>
<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>5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<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>5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.</td>
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<tr>
<td>207103, 05/09/2019</td>
<td>Palbociclib</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse</td>
<td>1 INDICATIONS AND USAGE</td>
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| 09/09/2019 | 207103, 09/09/2019           | Palbociclib (2)       | Oncology          | ERBB2      | Indications and Usage, Adverse Reactions, Clinical Studies | IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:  
  • an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or  
  • fulvestrant in patients with disease progression following endocrine therapy.  
  
6 ADVERSE REACTIONS  
6.1 Clinical Studies Experience  
Study 1: IBRANCE plus Letrozole  
Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy  
The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months. (…)  
Study 2: IBRANCE plus Fulvestrant  
Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy  
The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months. (…)  
Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer  
Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.  
14 CLINICAL STUDIES  
Study 1: IBRANCE plus Letrozole  
Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy  
Study 1 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. (…)  
Study 2: IBRANCE plus Fulvestrant  
Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy  
Study 2 (PALOMA-3) was an international, randomized, double-blind, parallel group, multicenter study of IBRANCE plus fulvestrant versus placebo plus fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…) |

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| 021969, 01/25/2019                     | Paliperidone | Psychiatry | CYP2D6 | Clinical Pharmacology | 12.3 Pharmacokinetics
Metabolism and Elimination
(…) Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. (…) |
| 021372, 09/18/2014                     | Palonosetron | Gastroenterology | CYP2D6 | Clinical Pharmacology | 12.3 Pharmacokinetics
Metabolism
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-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. |
| 125147, 06/29/2017                     | Panitumumab (1) | Oncology | EGFR | 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 2005050203, 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 2005050203 are limited to 656 patients with wild-type KRAS mCRC. The safety profile of Vectibix in patients with wild-type mCRC and mCRCC is similar with that seen in patients with wild-type KRAS mCRC. |
| 125147, 06/29/2017                     | Panitumumab (2) | Oncology | RAS | 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 (2.1.1)];
• As first-line therapy in combination with FOLFOX [see Clinical Studies (14.2)];
• As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy [see Clinical Studies (14.1)].
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 (2.1.1), Warnings and Precautions (5.2), and Clinical Pharmacology (12.1)]. |

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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](http://www.fda.gov/CompanionDiagnostics).

5 WARNINGS AND PRECAUTIONS

5.2 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with RAS-Mutant mCRC

Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereafter is referred to as "RAS" [see Indications and Usage (1.1), Dosage and Administration (2.1), Clinical Pharmacology (12.1), and Clinical Studies (14)]. Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of RAS mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing RAS mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents [see Indications and Usage (1.1), and Clinical Pharmacology (12.1)]. Additionally, in Study 20050203, 272 patients with RAS-mutant mCRC tumors received Vectibix in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with RAS-mutant mCRC who received Vectibix and FOLFOX versus FOLFOX alone [see Indications and Usage (1.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- (…) Increased Tumor Progression, Increased Mortality, or Lack of Benefit in RAS-Mutant mCRC [see Indications and Usage (1.1) and Warnings and Precautions (5.2)] (…)

6.1 Clinical Trials Experience

(…) Safety data are presented from two clinical trials in which patients received Vectibix: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 465) 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.

(…) Vectibix in Combination with FOLFOX Chemotherapy

The most commonly reported adverse reactions (≥ 20%) in patients with wild-type KRAS mCRC receiving Vectibix (8 mg/kg every 2 weeks) and FOLFOX therapy (N = 322) in Study 20050203 were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin (Table 2). Serious adverse reactions (≥ 2% difference between treatment arms) in Vectibix-treated patients with wild-type KRAS mCRC were diarrhea and dehydration. The commonly reported adverse reactions (≥ 1%) leading to discontinuation in patients with wild-type KRAS mCRC receiving Vectibix were rash, paresthesia, fatigue, diarrhea, acneiform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypokalemia, occurred in a patient who received Vectibix. (See Table 2) (…)

14 CLINICAL STUDIES

14.1 Recurrent or Refractory mCRC

The safety and efficacy of Vectibix was demonstrated in Study 20020408, an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum, and in Study 20080763, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type KRAS mCRC, and in Study 20100007, an open-label, multicenter, multinational, randomized trial of 377 patients with wild-type KRAS mCRC. (…) Study 20020408 (NCT00113763)

(…) The study results were analyzed in the wild-type KRAS subgroup where KRAS status was retrospectively determined using archived paraffin-embedded tumor tissue. KRAS mutations were detected in 427 patients (92%) of these, 243 (57%) had no detectable KRAS mutations in either codons 12 or 13. The hazard ratio for PFS in patients with wild-type KRAS mCRC was 0.45 (95% CI: 0.34-0.59) favoring the panitumumab arm. The response rate was 17% for the panitumumab arm and 0% for BSC. There were no differences in OS; 77% of patients in the BSC arm received panitumumab at the time of disease progression.

Study 20080763 (NCT01001377)

Study 20080763a was an open-label, multicenter, multinational, randomized (1:1) clinical trial, stratified by region (North America, Western Europe, and Australia versus rest of the world) and ECOG PS (0 and 1 vs 2) in patients with wild-type KRAS mCRC. (See Table 3 and Figure 1) (…) Study 20100007 (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 RA mCRC. (…)

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| 020987, 04/25/2019                     | Pantoprazole | Gastroenterology | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  
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 7.5 hours, AUC values increased to 5- to 7-fold in pantoprazole poor metabolizers (CYP2C19 *2/*2). Although these increases were no greater than those observed in 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/*2) metabolizers. Poor metabolizers exhibited approximately 10 fold lower apparent oral clearance compared to extensive metabolizers. For known pediatric poor metabolizers, a dose reduction should be considered. |
| 125511, 12/17/2018                     | Parathyroid Hormone | Ischemic Errors of Metabolism | CASR | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE  
NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Limitations of Use:  
• Because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone [see Warnings and Precautions (5.1)].  
• NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.  
• NATPARA was not studied in patients with post-surgical hypoparathyroidism.  
14 CLINICAL STUDIES  
Study in Patients with Established Hypoparathyroidism  
(…) Patients with hypoparathyroidism due to calcium-sensing receptor mutations were excluded from the trial. (…) |

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| 200301, 01/04/2017                     | Paroxetine    | Psychiatry       | CYP2D6    | Drug Interactions, Clinical Pharmacology | DRUG INTERACTIONS Drugs Metabolized by CYP2D6: (…) In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine Cmax values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine. (…)

| 210922, 08/10/2018                     | Patisiran     | Neurology        | TTR       | Adverse Reactions, Clinical Pharmacology, Clinical Studies | 6 ADVERSE REACTIONS (…) At baseline, 46% of patients were in Stage 1 of the disease and 53% were in Stage 2. Forty-three percent of patients had Val30Met mutations in the transthyretin gene; the remaining patients had 38 other point mutations. Sixty-two percent of ONPATTRO-treated patients had non-Val30Met mutations, compared to 48% of the placebo-treated patients. (…)

| 022465, 06/02/2020                     | Pazopanib (1) | Oncology         | UGT1A1    | Clinical Pharmacology             | 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Pazopanib can increase serum total bilirubin levels (see Warnings and Precautions (5.3)). In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. A pooled pharmacogenetic analysis of 236 Caucasian patients evaluated the TA-repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during pazopanib treatment. In this analysis, the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic susceptibility to Gilbert’s syndrome) was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes.

| 022465, 06/02/2020                     | Pazopanib (2) | Oncology         | HLA-B     | Clinical Pharmacology             | 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 > 3 X ULN (NCI CTCA Grade 2) occurred in 32% (42/133) of HLA-B*57:01 allele carriers and in 19% (39/210) of non-carriers and ALT > 5 X ULN (NCI CTCA Grade 3) occurred in 19% (25/133) of HLA-B*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)).

| 103849, 01/08/2019                     | Peginterferon Alfa-2b | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics A retrospective genome-wide association analysis of 1671 subjects (1604 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 rs8103142) 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)

| 125293, 07/13/2018                     | Pegloticase   | Rheumatology     | G6PD      | Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information | BOXED WARNING WARNING: ANAHYLAXIS 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 in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency (4, 5.3).

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| 12/25/14   | 06/24/2020            | Pembrolizumab  | Oncology         | BRAF        | Adverse Reactions, Clinical Studies | **6 ADVERSE REACTIONS**  
6.1 Clinical Trials Experience  
**Ipilimumab-Refractory Melanoma**  
The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. (...) |
| 14 CLINICAL STUDIES  
14.1 Melanoma  
**Ipilimumab-Naive Melanoma**  
(...) A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 58% White, 66% had no prior systemic therapy for metastatic disease, 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO 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 KEYTRUDA mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. (...)  
**Ipilimumab-Refractory Melanoma**  
(...) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. (...)  
(...) Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease. (...)  
**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 unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. (...)  
**Adjuvant Treatment of Resected Melanoma**  
(...) The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 82% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIa, 46% had stage IIb, 18% had stage III (1-3 positive lymph nodes), and 20% had stage IIc (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IgG assay. (...) |
| 12/25/14   | 06/24/2020            | Pembrolizumab  | Oncology         | CD274        | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | **1 INDICATIONS AND USAGE**  
1.2 Non-Small Cell Lung Cancer  
**KEYTRUDA**, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.  
**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.  
**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:  
† stage III when patients are not candidates for surgical resection or definitive chemoradiation, or  
* metastatic. |

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<td>KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor alterations should have disease progression on FDA-approved therapy for these alterations prior to receiving KEYTRUDA.</td>
<td>1.4 Head and Neck Squamous Cell Cancer</td>
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<td>KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).</td>
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<td>KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test [see Dosage and Administration (2.1)].</td>
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<td>KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.</td>
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<td>KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy if appropriate, HER2/neu-targeted therapy [see Clinical Studies (14.7)].</td>
<td>1.7 Urothelial Carcinoma</td>
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<td>KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy [see Clinical Studies (14.7)]. This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14.7)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
<td>1.9 Gastric Cancer</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after two or more prior lines of systemic therapy.</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.10)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.</td>
<td>1.11 Cervical Cancer</td>
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<td>KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression after one or more prior lines of systemic therapy.</td>
<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)].</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 (14.9)].</td>
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<td>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 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>14.1 Melanoma</td>
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<td>(…) 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 (IUO) assay. (…)</td>
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<td>The study population characteristics were: median age of 62 years (range: 18 to 89); 80% male; 96% White; 86% had no prior systemic therapy for metastatic disease; 69% ECOG PS of 0; 86% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO-approved test for the detection of MSI-H or dMMR is not currently available. (See Table 2)</td>
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- **Adjuvant Treatment of Resected Melanoma**
  - The study population characteristics were: median age of 54 years (range: 19 to 88); 25% age 65 or older; 60% male; 94% ECOG PS of 0 and 6% ECOG PS of 1.
  - Sixteen percent had stage III, 46% had stage IIIb, 18% had stage IIIc (1-3 positive lymph nodes), and 20% had stage IIIa (24 positive lymph nodes).
  - 50% were BRAF V600E mutation positive and 44% were BRAF wild-type.
  - 84% had PD-L1 positive melanoma with TPS ≥1% according to an IHC assay. (See Table 21) (…)
  - The study population characteristics were: median age of 64 years (range: 34 to 88); 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG performance status of 1; and 18% with history of brain metastases. Seventy-one percent had tumor PD-L1 expression TPS ≥1% (negative) (See Table 21) (…)

- **14.2 Non-Small Cell Lung Cancer**
  - First-line treatment of metastatic nonsquamous NSCLC with pembrolizumab.
  - The efficacy of KEYTRUDA in combination with pembrolizumab and investigator's choice of either paclitaxel or nab-paclitaxel chemotherapy was investigated in KEYNOTE-040 (NCT02754359), a randomized, multicenter, double-blind, placebo-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 <1% [negative] vs. TPS ≥1%). (See Table 35) (…)
  - The study population characteristics were: median age of 64 years (range: 34 to 88); 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG performance status of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% (negative). Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/L1 monoclonal antibody at the time of disease progression. (See Table 35) (…)

- **First-line treatment of metastatic squamous NSCLC with carboplatin and investigator’s choice of either paclitaxel or nab-paclitaxel chemotherapy.**
  - The efficacy of KEYTRUDA in combination with carboplatin and investigator’s choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-040 (NCT02754359), a randomized, multicenter, double-blind, placebo-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. 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 <1% [negative] vs. TPS ≥1%). (See Table 35) (…)
  - The study population characteristics were: median age of 64 years (range: 34 to 88); 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG performance status of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% (negative). Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/L1 monoclonal antibody at the time of disease progression. (See Table 35) (…)

- **First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and investigator’s choice of either paclitaxel or nab-paclitaxel chemotherapy.**
  - The efficacy of KEYTRUDA in combination with pemetrexed and investigator’s choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407 (NCT02775435), a randomized, multicenter, double-blind, placebo-controlled trial conducted in 529 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Seventy-two percent received Carboplatin and 12% were never smokers. (See Table 21) (…)

- **First-line treatment of metastatic squamous NSCLC with carboplatin and investigator’s choice of either paclitaxel or nab-paclitaxel chemotherapy.**
  - The efficacy of KEYTRUDA in combination with carboplatin and investigator’s choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407 (NCT02775435), a randomized, multicenter, double-blind, placebo-controlled trial conducted in 529 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Seventy-two percent received Carboplatin and 12% were never smokers. (See Table 21) (…)

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<td>14.1 Example Biomarker Name</td>
<td>KEYNOTE-024</td>
<td>The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 285 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. (…)</td>
<td>Previously treated NSCLC</td>
<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 progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit.</td>
<td>This study was designed to evaluate the efficacy and safety of KEYTRUDA in patients with PD-L1 CPS ≥10. (…)</td>
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<tbody>
<tr>
<td>125514, 06/24/2020</td>
<td>Pembrolizumab (3)</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 52 and Figure 12 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10. KEYNOTE-180 Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The baseline characteristics of these 35 patients were: median age of 65 years (range: 47 to 81), 51% age 65 or older, 71% male: 26% White and 69% Asian: 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. One hundred percent had M1 disease. The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8.37). Among the 7 responding patients, the DoR ranged from 2.4 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer. <strong>14.11 Cervical Cancer</strong> 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; 96% 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). (…) <strong>14.14 Renal Cell Carcinoma</strong> 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. (…)</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling
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| NDA/ANDA/BLA Number, Label Version Date | Drug | Therapeutic Area† | Biomarker‡ | Labeling Sections | Labeling Text*
|---------------------------------------|-------|------------------|------------|-----------------|--------------------------------------------------
| 125514, 06/24/2020 | Pembrolizumab (4) | Oncology | EGFR | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Non-Small Cell Lung Cancer
KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
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:
• stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
• metastatic.
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.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
NSCLC
First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy
The safety of KEYTRUDA in combination with pemetrexed and investigator’s choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (1:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations (see Clinical Studies (14.2), (…))
Previously Untreated NSCLC
The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC (see Clinical Studies (14.2)). Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator’s choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pembrolizumab or pemetrexed and carboplatin followed by optional pembrolizumab (n=312) or paclitaxel and carboplatin followed by optional pembrolizumab (n=303) every 3 weeks. Patients with EGFR

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| 125514, 06/24/2020 | Pembrolizumab (5) | Oncology | ALK | 1 INDICATIONS AND USAGE | or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. (…)

The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations (see Clinical Studies [14.2]).

**14 CLINICAL STUDIES**

14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic non-small NSCLC with pemetrexed and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, double-blind, 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 1HC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. (…)

Previous treatment with platinum-based chemotherapy, if applicable, was permitted (…)

The efficacy of KEYTRUDA was investigated in KEYNOTE-021 (NCT02095657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. (…)

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease. (…) The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease. (…)

1.2 Non-Small Cell Lung Cancer

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations. 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.

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:

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

NSCLC

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and investigator’s choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.2)]. (…)

Previously Untreated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC [see Clinical Studies (14.2)].

Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator’s choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. (…)

Previously Treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a randomized, multicenter, double-blind, 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 1HC 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. (…)

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease. (…)

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| 125514, 06/24/2020 | Pembrolizumab (6) | Oncology | Tumor Mutational Burden | Indications and Usage, Dosage and Administration, Clinical Studies | The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations [see Clinical Studies (14.2)]. 14 CLINICAL STUDIES 14.2 Non-Small Cell Lung Cancer First-line treatment of metastatic nonsquamous NSCLC with pembrolizumab and platinum chemotherapy The efficacy of KEYTRUDA in combination with pembrolizumab and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. (…) First-line treatment of metastatic NSCLC as a single agent KEYNOTE-042 The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage IIIB or IV 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. (…) 14.16 Tumor Mutational Burden-High Cancer KEYNOTE-010, a multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC who had progressed following platinum-containing chemotherapy, and, if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. (…) (…) The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 6% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-based regimen, 29% received two or more prior therapies for their metastatic disease. (…) 1 INDICATIONS AND USAGE 1.16 Tumor Mutational Burden-High Cancer KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) ≥10 mutations/megabase (mut/Mb) solid tumors, as determined by an FDA-approved test [see Dosage and Administration (2.1)], that have progressing following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.10)]. 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. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H Cancer, or TMB-H Cancer (…) For the TMB-H indication, select patients for treatment with KEYTRUDA as a single agent based on TMB-H status in tumor specimens [see Clinical Studies (14.16)]. For the MSI-H/dMMR indication, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens [see Clinical Studies (14.8)]. Because the effect of prior chemotherapy on test results for tumor mutational 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 specimen obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas. Information on FDA-approved tests for the detection of PD-L1 expression and TMB status is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of MSI-H or dMMR is not currently available. (See Table 2) 14 CLINICAL STUDIES 14.16 Tumor Mutational Burden-High Cancer The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with high tumor mutational burden (TMB-H) who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). (…) The statistical analysis plan pre-specified ≥10 and ≥13 mutations per megabase using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The major efficacy outcome measures were ORR and DoR in patients who received at least one dose of KEYTRUDA as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. In KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analysed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 152 (19%) had tumors identified as TMB-H, defined as TMB ≥10 mutations per megabase. Among the 102 patients with TMB-H advanced solid tumors, the study population characteristics were: median age of 61 years (range: 27 to 90). * 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. 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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 | PRECAUTIONS
Drug Interactions
Metabolism of a number of medications, including antipsychotics, antidepressants, beta-blockers, and antiarrhythmics, occurs through the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called “poor” metabolizers. Among other populations the prevalence is not known. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. In one study of 45 elderly patients suffering from dementia treated with perphenazine, the 5 patients who were prospectively identified as poor P450 2D6 metabolizers had reported significantly greater side effects during the first 15 days of treatment than the 40 extensive metabolizers, following which the groups tended to converge. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events. (…)
| 125409, 01/16/2020                     | Pertuzumab (1) | Oncology        | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Warnings and 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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<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Metastatic Breast Cancer</td>
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<td>14.2 Neoadjuvant Treatment of Breast Cancer</td>
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<td>TRYPHAENA</td>
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|                                       |       |                 |            |                   | CLEOPATRA (NCT0567195) 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 type of breast cancer (non-metastatic, metastatic), geographic region (Europe, North America, South America, and Asia), and prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment. (…)
|                                       |       |                 |            |                   | 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. (…)
|                                       |       |                 |            |                   | 14.3 Adjuvant Treatment of Breast Cancer |
|                                       |       |                 |            |                   | A two-arm non-randomized study (BERENICE, NCT02132949) was conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive 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. (…)

5 WARNINGS AND PRECAUTIONS
5.1 Left Ventricular Dysfunction
Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered [Dosage and Administration (2.3)]. (…)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Metastatic Breast Cancer (MBC)
(…) The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in Study 1. (…)
Adjuvant Treatment of Breast Cancer (APHINITY)
The adverse reactions described in Table 6 were identified in 4769 patients with HER2-positive early breast cancer treated in APHINITY. (…)

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‡ 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.

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<td>Phenytoin (1)</td>
<td>Neurology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>(…) 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 plasma 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. (…)</td>
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<td>010151, 06/16/2016</td>
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<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>(…) 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 plasma 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. (…)</td>
</tr>
<tr>
<td>010151, 06/16/2016</td>
<td>Phenytoin (3)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings</td>
<td>WARNINGS Serious Dermatologic Reactions Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. Diltain should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (see DRESS/Multorgan hypersensitivity below). 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, in patients using carbamazepine. Limited evidence suggests that HLA-B</em>1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.</td>
</tr>
</tbody>
</table>

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<tr>
<td>017473, 09/27/2011</td>
<td>Pimozide</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Precautions</td>
<td>The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.</td>
</tr>
<tr>
<td>018147, 05/03/2019</td>
<td>Piroxicam</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>211150, 08/14/2019</td>
<td>Pitolisant</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>203469, 01/10/2020</td>
<td>Ponatinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>1 INDICATIONS AND USAGE</td>
<td>Iclusig (ponatinib) is a kinase inhibitor indicated for the:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 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).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML [see Warnings and Precautions (5.7)].</td>
</tr>
</tbody>
</table>

|                                        |      |                   |            |                   | 5 WARNINGS AND PRECAUTIONS |
|                                        |      |                   |            |                   | 5.2 Venous Thromboembolism |
|                                        |      |                   |            |                   | Venous thromboembolic events occurred in 6% (25/449) of Iclusig-treated patients, including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients) with vision loss. In the phase 2 trial, the incidence of venous thromboembolism was 9% (3/302) 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% (13/267) 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)]. |
|                                        |      |                   |            |                   | 5.4 Hepatotoxicity |
|                                        |      |                   |            |                   | Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts. (…)
|                                        |      |                   |            |                   | 5.10 Hemorrhage |
|                                        |      |                   |            |                   | Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Iclusig in the phase 2 trial, with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% (4/449 and 4/449, respectively). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia [see Warnings and Precautions (5.13)]. Interrupt Iclusig for serious or severe hemorrhage and evaluate [see Dosage and Administration (2.3)]. |
|                                        |      |                   |            |                   | 5.13 Myelosuppression |
|                                        |      |                   |            |                   | Myelosuppression was reported as an adverse reaction in 59% (266/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Iclusig. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (…)
|                                        |      |                   |            |                   | 5.14 Tumor Lysis Syndrome |
|                                        |      |                   |            |                   | Two patients (1%) treated with Iclusig developed serious tumor lysis syndrome. One case occurred in a patient with advanced AP-CML and one case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig. |

|                                        |      |                   |            |                   | 6 ADVERSE REACTIONS |
|                                        |      |                   |            |                   | 6.1 Clinical Trial Experience |
|                                        |      |                   |            |                   | Previously Treated CML or Ph+ ALL |
|                                        |      |                   |            |                   | The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. (…)
|                                        |      |                   |            |                   | (…) The rates of treatment-emergent adverse reactions resulting in discontinuation were 19% in CP-CML, 12% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse reactions that led to treatment discontinuation was thrombocytopenia (4%). (See Table 5) (…)
|                                        |      |                   |            |                   | Laboratory Abnormalities |
|                                        |      |                   |            |                   | (…) Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (See Table 7) (…)

|                                        |      |                   |            |                   | 8 USE IN SPECIFIC POPULATIONS |
|                                        |      |                   |            |                   | 8.5 Geriatric Use |
|                                        |      |                   |            |                   | One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (40%) as compared with patients < 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a similar hematologic response rate (45%) as compared with patients < 65 years of age (44%). (…)

|                                        |      |                   |            |                   | 14 CLINICAL STUDIES |

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<td>022307, 03/28/2019</td>
<td>Prasugrel (1)</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<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]; blast phase CML; Philadelphia-positive acute lymphoblastic leukemia [BP-CML;Ph+ ALL]), resistance or intolerance (RII) to prior TKI therapy, and the presence of the T315I mutation. Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ ALL. The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). The trial enrolled 449 patients, of which 444 were eligible for efficacy analysis: 267 patients with CP-CML (RII 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 did not receive prior dasatinib or nilotinib. (See Table 11) (…) (…) The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 0.7 months (range: 0.4 to 5.5 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 MaHR for patients with AP-CML, BP-CML, and Ph+ ALL was 12.0 months (range: 1.2 to 52+ months), 6.0 months (range: 1.8 to 47.4+ months), and 3.2 months (range: 1.8 to 12.8+ months), respectively.</td>
</tr>
<tr>
<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.</td>
</tr>
<tr>
<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.</td>
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| 022307, 03/28/2019                    | Prasugrel (4) | Cardiology | CYP2B6 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY  
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.  

14 CLINICAL STUDIES  
(…) 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. (…) |
| 008316, 06/22/2017                    | Primaquine (1) | Infectious Diseases | G6PD | Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage | CONTRAINDICATIONS  
Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings).  

WARNINGS  
Hemolytic anemia and G6PD deficiency  
Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Primaquine should not be prescribed for patients with severe G6PD deficiency (see Contraindications).  
In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. Discontinue the use of primaquine phosphate promptly if signs suggestive of hemolytic anemia occur (darkening of the urine, marked fall of hemoglobin or erythrocytic count).  
Hemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia, and Oceania. People from these regions have a greater tendency to develop hemolytic anemia (due to a congenital deficiency of erythrocytic G6PD) while receiving primaquine and related drugs.  
Use in Pregnancy  
Safe usage of this preparation in pregnancy has not been established. Primaquine is contraindicated in pregnant women. Even if a pregnant woman is G6PD normal, the fetus may not be (see Contraindications).  

PRECAUTIONS  
Blood Monitoring  
Since anemia, methemoglobinemia, and leukopenia have been observed following administration of large doses of primaquine, the adult dosage of 1 tablet (= 15 mg base) daily for fourteen days should not be exceeded. In G6PD-normal patients it is also advisable to perform routine blood examinations (particularly blood cell counts and hemoglobin determinations) during therapy.  

ADVERSE REACTIONS  
Hematologic  
Leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.  

OVERDOSAGE  
Symptoms of overdosage of primaquine phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia, and anemia.  

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<td>Primaquine (2)</td>
<td>Infectious Diseases</td>
<td>CYB5R</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS Blood Monitoring (...) If primaquine phosphate is prescribed for an individual who has shown a previous idiosyncratic reaction to primaquine phosphate as manifested by hemolytic anemia, methemoglobinemia, or leukopenia, an individual with a family or personal history of hemolytic anemia or nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency, the person should be observed closely. In all patients, the drug should be discontinued immediately if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs.</td>
</tr>
<tr>
<td>007898</td>
<td>Probenecid</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Adverse Reactions</td>
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<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 (7.1)].</td>
</tr>
</tbody>
</table>

#### 5 WARNINGS AND PRECAUTIONS

5.4 Drug Interactions: Simultaneous Use with Inhibitors of Cytochrome P450 Isoenzymes 2D6 and 3A4

Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6 activity and to a somewhat lesser extent in other demographic groups. Drugs that inhibit these CYP pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP3A4; 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 [see Warnings and Precautions (5.4) and Drug Interactions (7.1)].

7.1 CYP2D6 and CYP3A4 Inhibitors

Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline) and CYP3A4 (such as ketoconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be expected to cause increased plasma levels of propafenone. The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with administration of propafenone may increase the risk of adverse reactions, including proarrhythmia. Therefore, simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided [see Warnings and Precautions (5.4) and Dosage and Administration (2)].

#### 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetic Metabolism

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize desipramine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers. As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers achieving concentrations about 3 to 4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics is linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is

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| 021438, 11/19/2013                     | Propranolol | Cardiology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism and Elimination
In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance to 4-hydroxy propranolol was significantly higher and to naphthoxyacetic acid was significantly lower in EMs than PMs. |
| 07/3644, 07/17/2014                    | Protriptyline | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS
Drugs Metabolized by Cytochrome P450 2D6
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced CYP2D6 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). (…).
| 08/3388, 02/02/2010                    | Quinidine | Cardiology | CYP2D6 | Precautions | PRECAUTIONS
… Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers". When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the case of prodrugs whose actions are actually mediated by P450IID6-produced metabolites (for example, codeine and hydrocodeine, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers. Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6. (…). |
| 02/1799, 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. |
| 02/1799, 06/19/2019                    | Quinine Sulfate (2) | Infectious Diseases | CYP2D6 | Drug Interactions | 7 DRUG INTERACTIONS
7.2 Effects of Quinine on the Pharmacokinetics of Other Drugs
Desipramine (CYP2D6 substrate)
Quinidine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. (…).
| 02/0973, 06/07/2018                    | Rabeprazole | Gastroenterology | CYP2C19 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS
Tacrolium
Potential for increased exposure to tacrolium, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3)
12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism
(R) CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug.
Drug Interaction Studies
Combined Administration with Antimicrobials
Sixteen healthy subjects genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg ACIPHEX delayed-release tablets, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. (…). Clopixogrel
Clopixogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects including CYP2C19 extensive and intermediate metabolizers receiving once daily administration of clopoxiogrel 75 mg concomitantly with placebo or with 20 mg ACIPHEX delayed-release tablets (n=36), for 7 days was
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<th>Biomarker²</th>
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<th>Labeling Text³</th>
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</table>
| 020815, 06/27/2018                     | Oncology  | ESR (Hormone Receptor) | Clinical Studies | Raltegravir, Oncology | EGFR Exon 19 Deletions or Exon 21 (L858R) Substitution Mutations – CYRAMZA in Combination with Erlotinib

Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

2 DOSAGE AND ADMINISTRATION
2.3 Recommended Dosage for Non-Small Cell Lung Cancer
EGFR Exon 19 Deletions or Exon 21 (L858R) Substitution Mutations – CYRAMZA in Combination with Erlotinib
- The recommended dosage of CYRAMZA is 10 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity.
- Refer to the prescribing information for erlotinib for dosage information.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Non-Small Cell Lung Cancer
CYRAMZA Administered in Combination with Erlotinib (RELAY)

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<tbody>
<tr>
<td>125477, 05/24/2020</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 non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion 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>
</tr>
<tr>
<td>103846, 12/12/2019</td>
<td>Rasburicase (1)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID 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 &lt;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)].</td>
</tr>
</tbody>
</table>
| 103846, 12/12/2007                    | Rasburicase (2) | Oncology | CYBSR | 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.

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<th>Biomarker†</th>
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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>203805, 02/13/2020</td>
<td>Regorafenib</td>
<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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.</td>
</tr>
<tr>
<td>209092, 01/21/2020</td>
<td>Ribociclib (1)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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.</td>
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<tr>
<td>209092, 01/21/2020</td>
<td>Ribociclib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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.</td>
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<tr>
<td>212726, 02/27/2020</td>
<td>Rimegepant</td>
<td>Anesthesiology</td>
<td>CYP2C9</td>
<td>12.3 Pharmacokinetics</td>
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<td>Other Specific Populations</td>
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<td>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 (12.3)).</td>
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<td>12.5 Pharmacogenetics</td>
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<td>CYP2C9 activity is reduced in individuals with genetic variants such as the CYP2C9<em>2 and CYP2C9</em>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.</td>
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<td>Other Pharmacokinetics</td>
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<td>Plasma concentrations of rimegepant, its major metabolite, 9-hydroxyrimegepant, and rimegepant plus 9-hydroxyrimegepant 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 rimegepant occurred at about 1 hour. Peak concentrations of 9-hydroxyrimegepant occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of rimegepant are reached in 1-7 days in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrimegepant are reached in 5-6 days (measured in extensive metabolizers).</td>
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<td>Absorption</td>
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<td></td>
<td>Rimegepant is well absorbed. The absolute oral bioavailability of rimegepant is 70% (CV=25%). The relative oral bioavailability of rimegepant 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.</td>
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<td>Plasma concentrations of rimegepant, its major metabolite, 9-hydroxyrimegepant, and rimegepant plus 9-hydroxyrimegepant 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 rimegepant occurred at about 1 hour. Peak concentrations of 9-hydroxyrimegepant occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of rimegepant are reached in 1-7 days in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrimegepant are reached in 5-6 days (measured in extensive metabolizers).</td>
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<td></td>
<td>CYP 2D6</td>
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<td>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 &quot;poor metabolizers&quot;) and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert rimegepant rapidly into 9-hydroxyrimegepant, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower rimegepant and higher 9-hydroxyrimegepant concentrations than poor metabolizers, the pharmacokinetics of rimegepant and 9-hydroxyrimegepant combined, after single and multiple doses, are similar in extensive and poor metabolizers. Rimegepant could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of rimegepant to 9-hydroxyrimegepant (see Drug Interactions (7)). This occurs with quinidine, giving essentially all recipients a rimegepant pharmacokinetic profile typical of poor metabolizers. The</td>
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<tbody>
<tr>
<td>103705, 03/13/2020</td>
<td>Rituximab</td>
<td>Oncology</td>
<td>MSH4A1 (CD20 antigen)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>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 (7)). It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (see Drug Interactions (7)). (…) Excretion Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9- hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.</td>
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<td>022406, 01/15/2019</td>
<td>Rivaroxaban</td>
<td>Cardiology</td>
<td>F5 (Factor V Leiden)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.3 Reduction in the Risk of Recurrence of DVT and/or PE (…). A total of 2270 patients were randomized and followed on study treatment for a mean of 260 days for the XARELTO and aspirin treatment groups. The mean age was approximately 59 years. The population was 56% male, 70% Caucasian, 14% Asian and 3% Black. In the EINSTEIN CHOICE study, 51% of patients had DVT only, 33% had PE only, and 16% had PE and DVT combined. Other risk factors included idiopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophic conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%). (…)</td>
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<td>020533, 11/02/2018</td>
<td>Ropivacaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNINGS  Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>020533, 11/02/2018</td>
<td>Ropivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS  Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<tr>
<td>021366, 11/09/2018</td>
<td>Rosuvastatin</td>
<td>Endocrinology</td>
<td>SLCO1B1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Disposition of 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 (SLCO1B1 521 T&gt;C). The frequency of this genotype (i.e., SLCO1B1 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established</td>
</tr>
<tr>
<td>209115, 05/10/2020</td>
<td>Rucaparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Ovarian Cancer • Rubraca is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. • Rubraca is indicated for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca (see Dosage and Administration [2.1]). 1.2 Metastatic Castration-Resistant Prostate Cancer with BRCA Mutations Rubraca is indicated for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic) associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen-directed therapy and a taxane-based chemotherapy (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)]. Information on the FDA-approved test for the detection of a tumor BRCA mutation in patients with ovarian cancer is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 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) [see Clinical Studies (14.2)]. An FDA-approved test for the detection of BRCA1/BRCA2 mutations in patients with mCRPC is not currently available. 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 277 patients with ovarian cancer treated in two openlabel, 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 152). (…)</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.
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<td>Rucaparib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Treatment of BRCA-mutated mCRPC after Androgen Receptor-directed Therapy and Chemotherapy</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
<td>The safety of Rucaparib 600 mg twice daily was evaluated in a single arm trial (TRITON2) (see Clinical Studies [14.2]). TRITON2 enrolled 209 patients with HRD-positive mCRPC, including 115 with BRCA-mutated mCRPC. Among the patients with BRCA-mutated mCRPC, the median duration of 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) (…)</td>
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<tr>
<td>Rucaparib (3)</td>
<td>Oncology</td>
<td>CYP1A2</td>
<td>Clinical Pharmacology</td>
<td>Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
<td>The efficacy of Rucaparib was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 10 (NCT01482715) and ARIEL2 (NCT01691344), in patients with advanced BRCA-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rucaparib 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and IRR according to RECIST v1.1. The median age of the patients was 59 years (range: 33 to 84), the majority were White (78%), and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had received 3 or more prior lines of platinum-based chemotherapy. There were 18/106 patients (17%) who had deleterious BRCA mutations detected in tumor tissue and not in whole blood samples. Tumor BRCA mutation status was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the companion diagnostic FoundationFocus™ CDx BRCA test, which is FDA approved for selection of patients for Rubraca treatment. (See Table 9) Response assessment by independent radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). Investigator-assessed ORR was 66% (62/92; 95% CI [54, 75]) in platinum-sensitive patients, 25% (9/36; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation. 14.2 Metastatic Castration-Resistant Prostate Cancer with BRCA mutations The efficacy of Rubraca was investigated in TRITON2 (NCT02952534), an ongoing multi-center, single arm clinical trial in patients with BRCA-mutated mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. There were 115 patients with either germline or somatic BRCA mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline by independent radiology review (IRR). (…) All 62 patients had a deleterious somatic or germline BRCA mutation detected from either central plasma (26%), central tissue (32%), or local (42%) testing. Of 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>
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<tr>
<td>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>14.1 Ovarian Cancer Maintenance Treatment of Recurrent Ovarian Cancer (…) Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564), and the FoundationFocus™ CDx BRCA LOH test (n=518). Of the samples evaluated with both tests, homologous recombination deficiency (HRD) positive status (as defined by the presence of a deleterious BRCA mutation or high genomic loss of heterozygosity) was confirmed by the FoundationFocus™ CDx BRCA LOH test for 94% (313/332) of HRD-positive patients determined by the CTA; and these, tumor BRCA LOH test for 99% (177/178) of BRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the BRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the BRCA patients had a germline BRCA mutation and 30% (56/186) had a somatic BRCA mutation. ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rubraca as compared with placebo in all patients, and in the HRD and BRCA subgroups. Results from a blinded independent radiology review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (with 22% of events) (see Table 8, Figures 1, 2, and 3)</td>
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<table>
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<td>761115, 04/22/2020</td>
<td>Sacituzumab Govitecan-hziy</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
<td>In TRITON2, MDS/AML was not observed in patients with mCRPC (n=209) regardless of homologous recombination deficiency (HRD) mutation [see Adverse Reactions (6.1)].</td>
</tr>
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</table>
| 213246, 06/09/2020 | Selpercatinib | Oncology | RET | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

RETEVMO 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).

1.2 RET-Mutant Medullary Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced 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

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection

Selected patients for treatment with RETEVMO based on the presence of a RET gene fusion (NSCLC or thyroid cancer) or specific RET gene mutation (MTC) in tumor specimens or plasma [see Clinical Studies (14)]. An FDA-approved test for the detection of RET gene fusions and RET gene mutations is not currently available. |

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**8 USE IN SPECIFIC POPULATIONS**

#### 8.4 Pediatric Use

The safety and effectiveness of RETEVMO have not been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients ages 12 years and older (see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)). The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age. The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications (see Indications and Usage (1)).

#### 14 CLINICAL STUDIES

**14.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer**

The efficacy of RETEVMO was evaluated in patients with advanced RET fusion-positive NSCLC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with advanced or metastatic NSCLC without prior systemic therapy in separate cohorts. Identification of a RET gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH). Adult patients received RETEVMO 160 mg orally twice daily until unacceptable toxicity or disease progression. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

Metastatic RET fusion-positive NSCLC previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. The median age was 61 years (range: 23 to 81); 59% were female; 52% were White, 38% Asian. 8% were Hispanic/Latino, 7% were Black, and 3.8% 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% chemotherapy, 2.3% anti-PD-1/PD-L1 therapy, and 3% radioiodine). RET mutation status

#### 8.6 Pediatric Use

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications (see Indications and Usage (1)).
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<td>020478, 04/27/2017</td>
<td>Sevoflurane</td>
<td>Anesthesiology</td>
<td>RYR1</td>
<td>Warnings</td>
<td>WARNINGS: Malignant hyperthermia is susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Sevoflurane can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, 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-aid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.</td>
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<td>205123, 11/09/2017</td>
<td>Simeprevir</td>
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<td>IFN3 (IL28B)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>A genetic variant near the gene encoding interferon-lambda-3 (IL28B), a C [cytosine] to T [thymine] substitution is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor. Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with OLYSIO-containing regimens (See Tables 12 and 13)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.2 OLYSIO in Combination with Sofosbuvir</td>
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<td>Adult Subjects with HCV Genotype 1 Infection</td>
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<td>(…). These 59 subjects had a median age of 57 years (range 27 to 68 years; with 2% above 65 years): 53% were male; 76% were White, and 24% Black or African American; 46% had a BMI greater than or equal to 30 kg/m²; the median baseline HCV RNA level was 6.75 log10 IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0-F1, F2 and F3, respectively, and 29% had METAVIR fibrosis score F4 (cirrhosis); 75% had HCV genotype 1a of which 41% carried Q80K polymorphism at baseline, and 25% had HCV genotype 1b; 14% had IL28B CC genotype, 64% IL28B CT genotype, and 22% IL28B TT genotype; 75% were prior null responders to Peg-IFN-alfa and RBV, and 25% were treatment-naive. OPTIMIST-1 was an open-label, randomized Phase 3 trial in HCV genotype 1-infected subjects without cirrhosis who were treatment-naive or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred 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 57 years (range 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, 20% Black or African American, and 16% Hispanic; 37% had a BMI ≥ 30 kg/m²; the median baseline HCV RNA level was 6.83 log10 IU/mL; 75% had HCV genotype 1a of which 40% had Q80K polymorphism at baseline, and 25% had HCV genotype 1b; 28% had IL28B CC genotype, 55% IL28B CT genotype, and 17% IL28B TT genotype; 74% were treatment-naive and 26% were treatment-experienced. (…) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 57/57 [100%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 19/19 [100%], respectively), and subjects with IL28B CC and non-CC genotypes (43/43 [100%] and 107/112 [96%], respectively).</td>
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<td>14.3 OLYSIO in Combination with Peg-IFN-alfa and RBV</td>
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|                                   |                     |                   |            |                   | Treatment Naïve Adult Subjects with HCV Genotype 1 Infection (…). In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the OLYSIO and placebo arms. In the pooled analysis of trials (QUEST 1 and QUEST 2), the 785 enrolled subjects had a median age of 47 years (range: 18 to 73 years; with 2% above 65 years); 56% were male; 91% were White, 7% Black or African American, 1% Asian, and 17% Hispanic; 23% had a body mass index (BMI) greater than or equal to 30 kg/m²; 78% had baseline HCV RNA levels greater than 800000 IU/mL; 74% had METAVIR fibrosis score F0, F1 or F2; 16% METAVIR fibrosis score F3; 40% had HCV genotype 1a, and 69% HCV genotype 1b; 29% had IL28B CC genotype, 56% 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 polymorphism S3.
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Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a; in QUEST 2, 69% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b.

Table 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-Naive East Asian Subjects with HCV Genotype 1 Infection (...)

The 304 subjects had a median age of 45 years (range: 23 to 64 years); 26% were male; 24% were Asian Chinese, 19% in South Korea); 3% had a body mass index (BMI) greater or equal to 30 kg/m²; 84% had baseline HCVRNA levels greater than 800000 IU/mL; 82% had METAVIR fibrosis score F0, F1 or F2, 12% METAVISION fibrosis score F3, and 6% METAVISION fibrosis score F4 (cirrhosis); 1% had HCVRNA genotype 1a, and 99% HCVRNA genotype 1b; less than 1% of the overall population had Q80K polymorphism at baseline; 79% had IL28B CC genotype, 20% IL28B CT genotype, and 1% IL28B TT genotype. Demographics and baseline characteristics were balanced across the OLYSIO 150 mg and placebo treatment groups. (...)

Adult Subjects with HCV Genotype 1 Infection who Failed Prior Peg-IFN-alfa and RBV Therapy (...)

Demographics and baseline characteristics were balanced between the OLYSIO and placebo treatment groups. The 393 subjects enrolled in the PROMISE trial had a median age of 52 years (range: 20 to 71 years; with 3% above 65 years); 66% were male; 94% were Asian Chinese, 2% Asian American, 2% Asian, and 2% Hispanic; 26% had a BMI greater than or equal to 30 kg/m²; 84% had baseline HCVRNA levels greater than 800000 IU/mL; 89% had METAVIR fibrosis score F0, F1, or F2, 14% METAVISION fibrosis score F3, and 6% METAVISION fibrosis score F4 (cirrhosis); 42% had HCVRNA genotype 1a, and 58% HCVRNA genotype 1b; 24% had IL28B CC genotype, 64% IL28B CT genotype, and 12% IL28B TT genotype; 32% of the overall population and 31% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. The prior IFN-based therapy was Peg-IFN-alfa-2b/RBV (68%) or Peg-IFN-alfa-2b/RBV/C (27%). (...)

SVR12 rates were higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCVRNA genotype/subtype, baseline HCVRNA load (less than or equal to 800000 IU/mL; greater than 800000 IU/mL), prior HCVRNA therapy, METAVISION fibrosis score, and IL28B genotype. Table 20 shows the SVR rates by METAVISION fibrosis score. (...)

In this trial, 66 subjects received 12 weeks of 150 mg OLYSIO in combination with Peg-IFN-alfa-2a and RBV for 48 weeks. These 132 subjects had a median age of 49 years (range: 23 to 64 years; with 1% above 65 years); 66% were male; 93% were White, 3% Black or African American, 2% Asian; 27% had a BMI greater than or equal to 30 kg/m²; 85% had baseline HCVRNA levels greater than 800000 IU/mL; 64% had METAVISION fibrosis score F0, F1, or F2, 18% METAVISION fibrosis score F3, and 18% METAVISION fibrosis score F4 (cirrhosis); 43% had HCVRNA genotype 1a, and 57% HCVRNA genotype 1b; 17% had IL28B CC genotype, 67% IL28B CT genotype, and 16% IL28B TT genotype (information available for 93 subjects); 27% of the overall population and 23% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. Forty percent (40%) of subjects were prior relapsers, 35% prior partial responders, and 25% prior null responders following prior therapy with Peg-IFN-alfa and RBV. Demographics and baseline characteristics were balanced between the 12 weeks 150 mg OLYSIO and placebo treatment groups. (See Table 21)

SVR4 rates were higher in the OLYSIO-treated subjects compared to subjects receiving placebo in combination with Peg-IFN-alfa and RBV, regardless of HCVRNA genotype/subtype, METAVISION fibrosis score, and IL28B genotype.

Subjects with HCVRNA-1 Co-infection: (...)

The 106 enrolled subjects in the C212 trial had a median age of 48 years (range: 27 to 67 years; with 2% above 65 years); 85% were male; 82% had a BMI greater than or equal to 30 kg/m²; 86% had baseline HCVRNA levels greater than 800000 IU/mL; 88% had METAVISION fibrosis score F0, F1, or F2, 19% METAVISION fibrosis score F3, and 13% METAVISION fibrosis score F4; 82% had HCVRNA genotype 1a, and 17% HCVRNA genotype 1b; 28% of the overall population and 34% of the subjects with genotype 1a had Q80K polymorphism at baseline; 27% had IL28B CC genotype, 50% IL28B CT genotype, and 23% IL28B TT genotype; 50% (n=53) were HCV treatment-naive subjects, 14% (n=15) prior relapsers, 9% (n=10) prior partial responders, and 26% (n=28) prior null responders. (...)

Adult Subjects with HCV Genotype 4 Infection (...)

The 107 enrolled subjects in the RESTORE trial had a median age of 49 years (range: 27 to 69 years; with 5% above 65 years); 79% were male; 72% were White, 28% Black or African American, and 7% Hispanic; 14% had a BMI greater than or equal to 30 kg/m²; 60% had baseline HCVRNA levels greater than 800000 IU/mL; 57% had METAVISION fibrosis score F0, F1 or F2, 14% METAVISION fibrosis score F3, and 29% METAVISION fibrosis score F4; 42% had HCVRNA genotype 4a, and 24% had HCVRNA genotype 4b; 8% had IL28B CC genotype, 54% IL28B CT genotype, and 35% IL28B TT genotype; 33% (n=35) were treatment-naïve HCVRNA subjects, 21% (n=22) prior relapsers, 9% (n=10) prior partial responders, and 37% (n=40) prior null responders. (...)

209884,
03/26/2019
Siponimod
Neurology
CYP2C9
Dosage and Administration, Contraindications, Drug Interactions, Use in Specific Populations, Clinical Pharmacology
2 DOSAGE AND ADMINISTRATION
2.1 Assessments Prior to First Dose of MAYZENT
Before initiation of treatment with MAYZENT, 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), 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 6. 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 2-mg maintenance dosage [see How Supplied/Storage and Handling (16.1, 16.2)]. (See Table 1)

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<td></td>
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<td>If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.</td>
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<td>2.3 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3</td>
<td>Maintenance Dosage</td>
<td></td>
<td>In patients with a CYP2C9 *(1/*3 or *2/*3) genotype, after treatment titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 5.</td>
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<td>Treatment Initiation</td>
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<td>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)</td>
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<td>If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.</td>
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<td>4 CONTRAINDICATIONS</td>
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<td>MAYZENT is contraindicated in patients who have:</td>
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<td></td>
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<td>• A CYP2C9*3/*3 genotype (see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5))</td>
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<td></td>
<td>7 DRUG INTERACTIONS</td>
<td>7.6 CYP2C9 and CYP3A4 Inducers</td>
<td></td>
<td>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.</td>
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<td>Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.</td>
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<td>Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/<em>3 and</em>2/*3 genotype (see Clinical Pharmacology (12.3)).</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
<td>8.6 CYP2C9 Genotype</td>
<td></td>
<td>Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9<em>3 (i.e., CYP2C9</em>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 (12.3)).</td>
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<td></td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.2 Pharmacodynamics</td>
<td></td>
<td>Immune System</td>
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<td>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.</td>
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<td>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)).</td>
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<td>Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. After stopping MAYZENT treatment, residual lowering effects on peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose (see Warnings and Precautions (5.1)).</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Drug Interaction Studies</td>
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<td>Siponimod as an Object of Interaction</td>
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<td>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.</td>
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<td>Coadministration of Siponimod with CYP2C9 and CYP3A4 Inhibitors</td>
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<td>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 of siponimod across different CYP2C9 genotypes, according to in silico evaluation (see Drug Interactions (7.5)).</td>
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<td>Coadministration of Siponimod with CYP3A4 Inducers</td>
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<td>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,ss and Cmax,ss by 57% and 45%, respectively in CYP2C9*1/*1 subjects. Rifampin and efavirenz (moderate CYP3A4 inducer) reduced the AiUC,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)).</td>
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<td>Oral Contraceptives</td>
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<td>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 not expected.</td>
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<td>5 WARNINGS AND PRECAUTIONS 5.6 G6PD Deficiency</td>
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<td>ASS1, CPS1, OTC (Urea Cycle Disorders)</td>
<td>Indications and Usage, Dosage and Administration</td>
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**12.5 Pharmacogenomics**

The CYP2C9 genotype has a significant impact on siponimod metabolism. After a single dose of 0.25 mg siponimod, AUCinf and AUClast was approximately 2- and 4-fold higher in subjects with the CYP2C9*2/*3 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 carriers (51 hours and 126 hours, respectively).

An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9*1/*1 and CYP2C9*1/*2) 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 resultant 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*1/*2 subjects is comparable to that of CYP2C9*1/*1 subjects, similar siponimod exposure is expected for both genotypes.

**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, cardiac or respiratory compromise), and those at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency), as they are at greater risk for potentially life-threatening adverse events related to the use of sodium nitrite. [see Warnings and Precautions (5.1 and 5.2)]

**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. (…)

**5.6 G6PD Deficiency**

Because patients with G6PD deficiency are at increased risk of a hemolytic crisis with sodium nitrite administration, alternative therapeutic approaches should be considered in these patients. Patients with known or suspected G6PD deficiency should be monitored for an acute drop in hematocrit. Exchange transfusion may be needed for patients with G6PD deficiency who receive sodium nitrite.

**5.7 Inborn Errors of Metabolism**

Sodium Phenybutyrate is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. (…)

Those who had IQ tests administered had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100% (14/14 patients tested); argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested); and carbamylphosphate synthetase deficiency, 57% (47 patients tested). (…) In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 88%. (…)

**INDICATIONS AND USAGE**

BUPHENYL® is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. (…)

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**DOSAGE AND ADMINISTRATION**

For oral use only.

The use of BUPHENYL® Tablets is indicated for children weighing more than 20 kg and for adults.

The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450–600 mg/kg/day in patients weighing less than 20 kg, or 9.9–13.0 g/m2/day in larger patients. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day). (…)

**NUTRITIONAL MANAGEMENT**

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| 204671, 10/23/2018 | Sofosbuvir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14 CLINICAL STUDIES 14.2 Clinical Trials in Subjects with Genotype 1 or 4 HCV Treated-Naïve Adults – NEUTRINO (Study 110) (…) SVR12 rates were 99% (89/90) in subjects with genotype 1 or 4 HCV and baseline IL28B C/C allele and 87% (200/230) in subjects with genotype 1 or 4 HCV and baseline IL28B non-C/C alleles. It is estimated that the SVR12 in patients who previously failed pegylated interferon and ribavirin therapy will approximate the observed SVR12 in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment (Table 9). The SVR12 rate in the NEUTRINO trial in genotype 1 subjects with IL28B non-C/C alleles, HCV RNA greater than 800,000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52). (See Table 9) 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 61 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 (99%) 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. 14.6 Clinical Trials in Subjects with Compensated Cirrhosis Genotype 2 HCV Infected Adults (ASTRAL-2) (…) Demographics and baseline characteristics were balanced across the two treatment groups. Of the 266 treated subjects, the median age was 58 years (range: 30 to 101); 68% of the subjects were male; 79% were White; 12% 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. (…) 14.7 Clinical Trials in Subjects without Compensated Cirrhosis Genotype 2 HCV Infected Adults (ASTRAL-3) (…) Demographics and baseline characteristics were balanced across the two treatment groups. Of the 552 treated subjects, the median age was 55 years (range: 23 to 81); 59% of the subjects were male; 88% were White; 7% were Black; 21% 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. (…) 14.8 Clinical Trials in Subjects with Compensated Cirrhosis Genotype 3 HCV Infected Adults (ASTRAL-2) (…) Demographics and baseline characteristics were balanced across the two treatment groups. Of the 552 treated subjects, the median age was 55 years (range: 23 to 81); 59% of the subjects were male; 88% were White; 7% were Black; 21% had a baseline body mass index at least 30 kg/m²; the proportions of patients with genotype 1, 2, 3, or 4 HCV infection were 74%; 10%; 11%; and 5% respectively; no subjects with genotype 5 or 6 HCV were treated with EPCLUSA; 77% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels of at least 144,000 IU/mL. (…) At the recommended dose of sodium phenylbutyrate, it is suggested that infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period. Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake. From 4 months to 1 year of age, it is recommended that the infant receive at least 1.4 g/kg/day, but 1.7 g/kg/day is advisable. From 1 to 3 years of age, the protein intake should not be less than 1.2 g/kg/day. 1.4 g/kg/day is advisable for children during this period. For neonatal-onset patients with carbamylphosphate synthetase deficiency or ornithine transcarbamylase deficiency who are at least 6 months of age, it is recommended that the daily protein intake be equally divided between natural protein and supplemental essential amino acids. Patients with argininosuccinic acid synthetase deficiency and those with late-onset disease (partial deficiencies, including females heterozygous for ornithine transcarbamylase), initially may receive a diet containing the age-determined minimal daily natural protein allowance. The protein intake may be increased as tolerated and determined by plasma glutamine and other amino acid levels. However, many patients with partial deficiencies avoid dietary protein. Citrulline supplementation is required and recommended for patients diagnosed with neonatal-onset deficiency of carbamylphosphate synthetase or ornithine transcarbamylase; citrulline daily intake is recommended at 0.17 g/kg/day or 3.8 g/m²/day. The free-base form of arginine may be used instead of citrulline in patients with milder forms of carbamylphosphate synthetase and ornithine transcarbamylase deficiency (daily intake is recommended at 0.17 g/kg/day or 3.8 g/m²/day). Arginine supplementation is needed for patients diagnosed with deficiency of argininosuccinic acid synthetase; arginine (free base) daily intake is recommended at 0.4-0.7 g/kg/day or 8.8-15.4 g/m²/day. * 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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| 007073, 03/04/2014                     | Sulfasalazine (2) | Gastroenterology | Nonspecific (NAT) | Clinical Pharmacology | CLINICAL PHARMACOLOGY Pharmacokinetics
Metabolism: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to S-hydroxy sulfapyridine (SPOH) and N-acetyl-S-hydroxy sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-S-amino salicylic 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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| 210607, 08/08/2018 | Tafenoquine | Infectious Diseases | G6PD | Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information | 2 DOSAGE AND ADMINISTRATION

2.1 Tests to be Performed Prior to ARAKODA Dose Initiation
All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA [see Contraindications (4), Warnings and Precautions (5.1)].

4 CONTRAINDICATIONS
ARAKODA is contraindicated in:
• patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia [see Warnings and Precautions (5.2)].
• breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown [see Warnings and Precautions (5.3), Use in Specific Populations (8.2)].

5 WARNINGS AND PRECAUTIONS
5.1. Hemolytic Anemia
Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA [see Contraindications (4)]. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status [see Contraindications (4)]. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients [see Adverse Reactions (6.1)]. Monitor patients for clinical signs or symptoms of hemolysis [see Warnings and Precautions (5.6)]. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur.

5.2 G6PD Deficiency in Pregnancy and Lactation
Potential Harm to the Fetus
The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Use in Specific Populations (8.1 and 8.3)].

Potential Harm to the Breastfeeding Infant
A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown.

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<td>Talazoparib</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>unknown (see Contraindications (4)). Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose (see Use in Specific Populations (8.2)).</td>
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8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy Risk Summary
The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Warnings and Precautions (5.2)]. (…)

8.2 Lactation Risk Summary
A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown (see Contraindications (4) and Clinical Considerations). There is no information regarding the presence of ARAKODA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition. Clinical Considerations
Check the infant’s G6PD status before maternal breastfeeding commences. If an infant is G6PD deficient, exposure to ARAKODA during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency or whose G6PD status is unknown, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose of ARAKODA.

8.3 Females and Males of Reproductive Potential
Contraception
ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus [see Warnings and Precautions (5.2). Use in Specific Populations (8.1)]. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA.

17 PATIENT COUNSELING INFORMATION
G6PD Testing and Hemolytic Anemia
Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia [see Warnings and Precautions (5.1)].

Lactation
Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose [see Contraindication (4), Warnings and Precautions (5.2). Use in Specific Populations (8.2)].

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<td>Talazoparib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) mutation (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms. (…)</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 subpopulation. The combination treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving anastrozole 1 mg and tamoxifen 20 mg monotherapy, respectively. (…)</td>
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<td>Prothrombin (F2)</td>
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<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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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-negative 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 p <0.00001).** The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (log-rank p = 0.00001).  
- **With negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.3% for tamoxifen vs. 73.3% for control (log-rank p <0.00001).** The recurrence-free rate at 10 years was 79.2% for tamoxifen vs. 63.4% for control (log-rank p <0.00001).  
- **Who received 1 year or less, 2 years, or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17%, and 26%, respectively (2p <0.003).** The corresponding reductions in breast cancer recurrence were 21%, 29%, and 47% (2p = 0.00001).  

Results in patients with ER-poor breast cancer:  
- **Benefit is less clear for women with ER-poor breast cancer in whom the proportional reduction in recurrence was 10% (2p = 0.007) for all durations taken together, or 9% (2p = 0.02) if contralateral breast cancers are excluded.** The corresponding reduction in mortality was 6% (not significant).  

**Node-positive: Individual Studies**  
- In the Hubay study, patients with a positive (more than 3 fmoI) 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 fmoI or greater clearly benefited, while survival results were poorer in women with both estrogen and progesterone receptor levels less than 10 fmoI. 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. (...)  
- In a small substudy (N = 81) of the NSABP -1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations associated with tamoxifen clearance from plasma. (…)  

**Node-negative: Individual Studies**  
- NSABP B-14, a prospective, double-blind, randomized study, compared another formulation of tamoxifen to placebo as adjuvant therapy in women with axillary node-negative, estrogen-receptor positive (≥10 fmoI/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 age 50 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.  

**Anastrozole Adjuvant Trial (ATAC): Arimidex, Tamoxifen, Alone or in Combination**  
- Study of Anastrozole Compared to Tamoxifen for Adjuvant Treatment of Early Breast Cancer  
- A trial was conducted in 9,366 postmenopausal women with operable breast cancer who were randomized to receive adjuvant treatment with either anastrozole 1 mg daily, another formulation of tamoxifen 20 mg daily, or a combination of these two treatments for 5 years or until recurrence of the disease. At a median follow-up of 33 months, the combination of anastrozole and tamoxifen did not demonstrate any efficacy benefit when compared to tamoxifen alone in all patients, as well as in the hormone receptor-positive subgroup. The combination treatment arm was discontinued from the trial (see Drug Interactions (7.1) and Clinical Pharmacology (12.3)). Refer to the full prescribing information for anastrozole tablets for additional information on this trial. (...)  

**14.4 Reduction in Breast Cancer Incidence in Women at High Risk**  
- Breast Cancer Prevention Trial (NSABP-P-1)  
- (...) Table 9 describes the characteristics of the breast cancers in the NSABP-P-1 trial in women at high risk for breast cancer. Tamoxifen decreased the incidence of small estrogen receptor-positive tumors, but did not alter the incidence of estrogen receptor-negative tumors or larger tumors. (See Table 9) (...)  

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| 020579, 01/23/2019                     | Tamsulosin | Urology | CYP2D6 | Warnings and Precautions, Adverse Interactions, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS
5.2 Drug Interactions
Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6. FLOMAX capsules 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. FLOMAX capsules should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terbinafine) 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)].

7 DRUG INTERACTIONS
7.1 CYP2D6 Inhibition
Strong and Moderate Inhibitors of CYP3A4 or CYP2D6
Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) and tamsulosin by a factor of 1.3 and 1.6, respectively [see Warnings and Precautions (5.2) and Drug Interactions (7.1)]. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when FLOMAX 0.4 mg is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, FLOMAX 0.4 mg capsules should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Drug Interactions
CYP2D6 Inhibition
Strong and Moderate Inhibitors of CYP3A4 or CYP2D6
The effects of paroxetine (a strong inhibitor of CYP2D6) at 20 mg once daily for 9 days on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range 23 to 47 years). Concomitant treatment with paroxetine resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively [see Warnings and Precautions (5.2) and Drug Interactions (7.1)].

201917, 10/26/2013                        | Telaprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology, Clinical Studies | 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 peginterferon alfa and ribavirin (RR). The 2979860 was genotyped in 454 of 1088 subjects in Trial T108 (treatment-naive) and 537 of 662 subjects in Trial C216 (previously treated) [see Clinical Studies (14.2 and 14.3) for trial descriptions]. SVR rates tended to be lower in subjects with the CT and TT genotypes compared to the CC genotype, particularly among treatment-naive subjects receiving PR48 (Table 9). Among both treatment-naive and previous treatment failures, subjects of all IL28B genotypes appeared to have higher SVR rates with regimens containing INC/VEK. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the subtrial population relative to the overall trial population. In Trial C211, all subjects were prospectively tested for IL28B variants; there were no clinically relevant differences in SVR12 responses between q8h and twice-daily dosing within the genetic subgroups. (See Table 9)

14 CLINICAL STUDIES
14.2 Treatment-NAive Adults
Telaprevir (OPTIMIZ2)
SVR rates were similar for the T12 (twice daily) vs PR and T12 (q8h) vs 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.

| 021894, 09/13/2017 | Tetrabenazine | Neurology | CYP2D6 | Dosage and Administration, 2.2 Individualization of Dose | 2 DOSAGE AND ADMINISTRATION

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<td>Thioguanine (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Warnings, Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td>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). The dosage 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)]. 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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**012429, 05/23/2018**

Thioguanine (1)

Oncology

TPMT

Dosage and Administration

... 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 TPMT1 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.

**WARNINGS**

... Evaluate patients with repeated severe myelosuppression for thioguanine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. Patients with homozygous TPMT or NUDT15 deficiency may require substantial dosage reductions. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulfasalazine.

**PRECAUTIONS**

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| 012429, 05/23/2018                     | Thioguanine (2) | Oncology | NUDT15 | Dosage and Administration, Warnings, Precautions, Clinical Pharmacology | DOSAGE AND ADMINISTRATION

...Patients with homoyzous 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 homoyzous TPMT or NUDT15 deficiency. Most patients with homoyzous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. Patients who are homoyzous for both TPMT and NUDT15 may require more substantial dosage reductions. Reduce the dosage based on tolerability.

WARNINGS

...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 homoyzous TPMT or NUDT15 deficiency require substantial dosage reductions. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.

PRECAUTIONS

Laboratory Tests

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression. (see WARNINGS).

CLINICAL PHARMACOLOGY

Metabolism and Genetic Polymorphism

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozyzous for either TPMT or NUDT15, 50-90%; heterozyzous for both TPMT and NUDT15, 30-50%; homoyzous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozyzous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozyzous 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 lossof-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.

011808

Thiouridine (2) | Psychiatry | CYP2D6 | Contraindications, Warnings, Precautions | Labeling not electronically available on Drugs@FDA

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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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| 022433, 04/03/2019                     | Ticagrelor | Cardiology | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
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. |
| 207961, 01/01/2020                     | Tipiracil and Trifluridine (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Metastatic Gastric Cancer
LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy, including a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy. |
| 207961, 01/01/2020                     | Tipiracil and Trifluridine (2) | Oncology | RAS | Indications and Usage, Clinical Studies | 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 fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. |
| 018894                                | Tolazamide | Endocrinology | G6PD | Precautions | Labeling not electronically available on Drugs@FDA |
| 010670                                | Tolbutamide | Endocrinology | G6PD | Precautions | Labeling not electronically available on Drugs@FDA |
| 021228, 07/13/2018                    | Tolterodine | Urology | CYP2D6 | Warnings and Precautions, Drug Interactions, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS
5.9 Use in Patients with Congenital or Acquired QT Prolongation
In a study of the effect of tolterodine immediate release tablets on the QT interval [see CLINICAL PHARMACOLOGY (12.2)], the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EM). 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 (EMs), resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine [see CLINICAL PHARMACOLOGY (12.1)]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [see CLINICAL PHARMACOLOGY (12.1)]. |

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<td>020497, 05/12/2017</td>
<td>Toremifene</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>020281, 04/08/2019</td>
<td>Tramadol</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Boxed Warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Patient</td>
<td>BOXED WARNING</td>
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</table>

**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

Cardiac Electrophysiology

The effect of 2 mg BID and 4 mg BID of DETROL immediate release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18–55 years. Study subjects (apart from an 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). (…) Tolterodine’s effect on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QTc interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study. (…)

#### 12.3 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 dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as “extensive metabolizers.” Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and 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 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. (…)

### 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 estrogen-receptor (ER) unknown metastatic breast cancer. (…)

### 5 WARNINGS AND PRECAUTIONS

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<td>Counseling Information</td>
<td>5.4 Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children</td>
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<td>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 may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:</td>
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<td>• ULTRAM is contraindicated for all children younger than 12 years of age [see Contraindications (4)].</td>
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<td>• ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)].</td>
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<td>• 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.</td>
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<td>• 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)].</td>
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<td>Nursing Mothers</td>
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<td>ULTRAM 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 (8.2)].</td>
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<td>CYP2D6 Genetic Variability: Ultra-rapid metabolizer</td>
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<td>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)]. Therefore, individuals who are ultra-rapid metabolizers should not use ULTRAM.</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.2 Lactation</td>
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<td>Risk Summary</td>
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<td>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.</td>
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<td>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 and mu opioid receptor binding [see Clinical Pharmacology (12)].</td>
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<td>Purified studies have shown no effect of 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. Women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ULTRAM [see Warnings and Precautions (5.4)].</td>
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<td>8.4 Pediatric Use</td>
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<td>The safety and effectiveness of ULTRAM in pediatric patients have not been established.</td>
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<td>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 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:</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>(...) 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.</td>
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1 INDICATIONS AND USAGE
1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
MEKINIST® is indicated, as a single agent in BRAF-inhibitor treatment-naïve patients or in combination with dabrafenib, 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)].

1.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma
MEKINIST is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see Dosage and Administration (2.1)].

1.3 BRAF V600E Mutation-Positive Metastatic NSCLC
MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1)].

1.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer
MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)].

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Melanoma
• Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST as a single agent or in combination with dabrafenib [see Clinical Studies (14.1), (14.2)].
• Information on FDA-approved tests for the detection of BRAF V600E mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics, NSCLC [see Clinical Studies (14.3)].
• Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.3)].
• Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics, ATC [see Clinical Studies (14.4)].

2.2 Dose
• 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.

2.3 Administration
• MEKINIST is administered as a single agent [see Clinical Studies (14.1)].

3 ADVERSE REACTIONS
3.1 Clinical Trials Experience
Unresectable or Metastatic BRAF V600E Mutation Positive Melanoma
MEKINIST Administered as a Single Agent
Table 3 presents adverse reactions identified from analyses of the METRIC study, a randomized, open-label trial of patients with BRAF V600E or V600K mutation-positive melanoma receiving MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine 1,000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 every 3 weeks) [see Clinical Studies (14.1)].

3.2 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)].

3.3 Metastatic, BRAF V600E Mutation-Positive NSCLC
The safety of MEKINIST when administered with dabrafenib was evaluated in 43 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928). (…) Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC) ...

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<td>The safety of MEKINIST when administered with dabrafenib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). (…)</td>
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**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

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

**12.3 Pharmacokinetics**

The pharmacokinetics (PK) of trametinib were characterized following single- and repeat-oral administration in patients with solid tumors and BRAF V600 mutation-positive metastatic melanoma. (…)"
Table of Pharmacogenomic Biomarkers in Drug Labeling

<table>
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<th>Drug</th>
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<th>Biomarker†</th>
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<th>Labeling Text</th>
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<td>204114, 06/23/2020</td>
<td>Trametinib (2)</td>
<td>Oncology</td>
<td>G6PD</td>
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<td>MEKINIST with Dabrafenib</td>
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<tr>
<td>204114, 06/23/2020</td>
<td>Trametinib (3)</td>
<td>Oncology</td>
<td>RAS</td>
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<td>Non-Cutaneous Malignancies</td>
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<tr>
<td>103792, 11/29/2018</td>
<td>Trastuzumab (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>Adjuvant Breast Cancer</td>
</tr>
</tbody>
</table>

In a subgroup analysis of patients with retrospectively centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncimmune™ Dx Target Test, the ORR results were similar to those presented in Table 14.

14.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer

The safety and efficacy of MEKINIST administered with dabrafenib was evaluated in Study BRF117019 (NCT02034110), an activity-estimating, nine-cohort, multi-center, non-randomized, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unsectectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. (…)

14.5 Lack of Clinical Activity in Metastatic Melanoma Following BRAF-Inhibitor Therapy

The clinical activity of MEKINIST as a single agent was evaluated in a single-arm, multicenter, international trial in 40 patients with BRAF V600E or V600K mutation-positive, unsectectable or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received MEKINIST at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity. The median age was 58 years, 63% were male, all were White, 98% had baseline ECOG PS of 0 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No patient achieved a confirmed partial or complete response as determined by the clinical investigators.

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</table>

### 14 CLINICAL STUDIES

#### 14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women. In the 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 center (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 4
    - In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH only) as determined at a central laboratory.

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 subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +IHC unknown subgroups. (See Table 10) (…)

#### 14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled trial in combination with chemotherapy (Study 5, n = 449 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 immunochemical assessment of tumor tissue performed by a central testing lab.

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 chemotherapeutic regimens for metastatic disease. (…)

Study 6 was a multicenter, randomized, open-label clinical trial conducted in 222 patients with metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. (…)

#### 14.3 Metastatic Gastric Cancer

The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 3084 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 fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%). (…)

The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), 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 = 2223), 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 = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2446), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.81). (See Table 9) (…)

#### 14.4 Adjuvant Breast Cancer

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 surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), 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 = 2223), 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 = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2446), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.81). (See Table 9) (…)

**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 use in the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2446), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.81). (See Table 9) (…)

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<td>Trimetoprim</td>
<td>Inborn Errors of Metabolism</td>
<td>ACA-DVL, CYP12, HADHA, HADHB (Long-Chain Fatty Acid Oxidation Disorders)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>016792, 07/17/2014</td>
<td>Tafamidis</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>Drugs Metabolized by P450 2D6</td>
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<td>213411, 04/17/2020</td>
<td>Trimetoprim</td>
<td>Inborn Errors of Metabolism</td>
<td>ACA-DVL, CYP12, HADHA, HADHB (Long-Chain Fatty Acid Oxidation Disorders)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<tr>
<td>205382, 06/06/2019</td>
<td>Trimetoprim</td>
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<td>ACA-DVL, CYP12, HADHA, HADHB (Long-Chain Fatty Acid Oxidation Disorders)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>211675, 08/16/2019</td>
<td>Trimetoprim</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>Ustekinumab</td>
<td>Dermatology and Gastroenterology</td>
<td>IL12A, IL12B, IL23A</td>
<td>Warnings and Precautions</td>
<td>5 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, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>018081, 02/21/2019</td>
<td>Valproic Acid (1)</td>
<td>Neurology</td>
<td>POLG</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING</td>
</tr>
</tbody>
</table>

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

Pharmacokinetic Studies
Pharmacokinetic studies in healthy volunteers given upadacitinib revealed that CYP3A4 is the primary CYP enzyme responsible for upadacitinib metabolism. Upadacitinib plasma exposure is increased by 68% in the presence of a CYP2D6 inhibitor compared to healthy volunteers. No clinically significant changes were observed in pharmacokinetics of upadacitinib when co-administered with CYP3A4 inhibitors.

5 WARNINGS AND PRECAUTIONS
5.2 Theoretical Risk for Vulnerability to Particular Infections
Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including monophystris strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

8 USE IN SPECIFIC POPULATIONS
8.6 CYP2D6 Poor Metabolizers
Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

7 WARNINGS AND PRECAUTIONS
7.2 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 or CYP3A4 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking 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)].

12 CLINICAL PHARMACOLOGY
12.2 Pharmacokinetic
Cardiac Electrophysiology
(…) INGREZZA may be contraindicated in patients known to have mitochondrial disorders caused by mutations of the mitochondrial DNA polymerase γ (POLG) gene (e.g., Alpers-Huttenlocher Syndrome). Dapoxetine 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 mitochondrial disorder, Dapoxetine should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Dapoxetine 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)].

4 CONTRAINDICATIONS
(…) Dapoxetine is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder [see Warnings and Precautions (5.1)]. (…)
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<tr>
<td>018081, 02/21/2019</td>
<td>Valproic Acid (2)</td>
<td>Neurology</td>
<td>Nonspecific (Urea Cycle Disorders)</td>
<td>Contraindications, Warnings and Precautions</td>
<td>4 CONTRAINDICATIONS (...) Depakene is contraindicated in patients with known urea cycle disorders [see Warnings and Precautions (5.6)].</td>
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<tr>
<td>202429, 05/18/2020</td>
<td>Vemurafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
<td>1 INDICATIONS AND USAGE 1.1 Unresectable or Metastatic Melanoma ZELBORAF® is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)]. 1.2 Erdheim-Chester Disease ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Confirm the presence of BRAF V600E mutation in melanoma tumor specimens prior to initiation of treatment with ZELBORAF [see Warnings and Precautions (5.2)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 5 WARNINGS AND PRECAUTIONS 5.2 Tumor Promotion in BRAF Wild-Type Melanoma In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation in tumor specimens prior to initiation of ZELBORAF [see Indications and Usage (1) and Dosage and Administration (2.1)]. 5.5 QT Prolongation Concentration-dependent QT prolongation occurred in an uncontrolled, open-label QT sub-study in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [see Clinical Pharmacology (12.2)]. (...)</td>
</tr>
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<td>5 WARNINGS AND PRECAUTIONS Other Malignancies</td>
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<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS Other Malignancies</td>
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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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)].

6.2 Postmarketing Experience

This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 [see Clinical Studies (14)].
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<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Progression of pre-existing chronic myelomonocytic leukemia with NRAS mutation [see Warnings and Precautions (5.1)]. (…)</td>
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<td>Chromosome 17p</td>
<td>Clinical Studies</td>
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<td>14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy</td>
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<td>(…) A total of 432 patients were randomized, 216 to each study arm. Baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, 67% were male, 36% and 43% were Binet stage B and C, respectively, and 88% had Eastern Cooperative Oncology Group (ECOG) performance status &lt;2. 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 10%, 11q deletion in 19%, and unmutated IgVH in 57%. (See Table 21) (…)</td>
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<td>(…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (See Table 21) (…)</td>
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<td>Monotherapy</td>
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<td>The efficacy of VENCELEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies. Study M13-982 The efficacy of VENCELEXTA was established in study M13-982 (NCT01889186), an open-label, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCELEXTA treatment. (See Table 23) (…)</td>
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<td>Study M12-175 (NCT01328626) was a multicenter, open-label trial that enrolled previously treated patients with CLL or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients (59 with CLL, 8 with SLL) who had received a 400 mg daily dose of VENCELEXTA. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months). The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% of patients had aCLc &gt;25 x 109/L, 33% had documented unmutated IgVH, and 21% had documented 17p deletion. (…)</td>
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<td>Of the 127 patients treated (91 with prior ibrutinib, 36 with prior ibratalisib), 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 &gt;25 x 109/L, 57% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)</td>
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<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 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) Study M14-387 Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m² was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26)</td>
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<td>FLT3</td>
<td>Clinical Studies</td>
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<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 Monobol) is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified. 6 ADVERSE REACTIONS Integrated Summary of Safety in Relapsed and/or Refractory Ph- Acute Lymphoblastic Leukemia Marqibo, at a dose of 2.25 mg/m² weekly, was studied in a total of 83 patients in two trials: study 1 and study 2. Adverse reactions were observed in 100% of patients. The most common adverse reactions (&gt;30%) were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%).</td>
</tr>
</tbody>
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| 021266, 04/30/2019                     | Voriconazole       | Infectious Diseases | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 [see Drug Interactions (7)]. In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCr) than their homozygous extensive metabolizer counterparts. (…)

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<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION. 2.6 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors. The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., buspirone, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued. [see Drug Interactions (7.3)].</td>
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<td>213137, 11/25/2019</td>
<td>Voxelotor</td>
<td>Hematology</td>
<td>HBB</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics. Metabolism and Elimination. Voxelotor is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of voxelotor to its major, pharmaceutically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the voxelotor plasma concentration of extensive metabolizers. (…)</td>
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<td>009218, 08/14/2017</td>
<td>Warfarin (1)</td>
<td>Hematology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Drug Interactions, Clinical Pharmacology</td>
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<td>VKORC1</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.3 Initial and Maintenance Dosing The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by: • Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities • Genetic factors (CYP2C9 and VKORC1 genotypes) [see Clinical Pharmacology (12.5)] (…) Dosing Recommendations without Consideration of Genotype Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see Clinical Pharmacology (12.5)]. If the patient’s CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9*1/*1, *2/*2, <em>2/<em>3, and <em>3/<em>3 may require more prolonged time (&gt;2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants. (See Table 1) 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics CYP2C9 and VKORC1 Polymorphisms The S-enantiomer of warfarin is mainly metabolized to 7-hydroxylwarfarin 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>
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<td>Hematology</td>
<td>PROS1</td>
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