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

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

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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>
| 020977, 03/20/2017                      | Abacavir    | Infectious Diseases | HLA-B      | Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions | BOXED WARNING WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY Hypersensitivity Reactions Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with ZIAGEN® (abacavir). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele [see Warnings and Precautions (5.1)]. ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients [see Contraindications (4), Warnings and Precautions (5.1)]. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible [see Contraindications (4), Warnings and Precautions (5.1)]. Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity [see Warnings and Precautions (5.1)]. (…)

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

4 CONTRAINDICATIONS
ZIAGEN is contraindicated in patients:
• who have the HLA-B*5701 allele [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir). These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with ZIAGEN (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment [see Adverse Reactions (6.1)]. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making. Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with ZIAGEN:
• All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment.
• ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
• Before starting ZIAGEN, review medical history for prior exposure to any abacavir containing product. NEVER restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
• To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
• If a hypersensitivity reaction cannot be ruled out, do not restart ZIAGEN or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death, can occur within hours.
• If a hypersensitivity reaction is ruled out, patients may restart ZIAGEN. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reintroducing abacavir therapy. Therefore, reintroduction of ZIAGEN or any other abacavir containing product is recommended only if medical care can be readily accessed.
• A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

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<td></td>
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<td>Reactions, Clinical Studies</td>
<td>• in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. • 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.</td>
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6 ADVERSE REACTIONS

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

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

MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician’s choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm. (…) MONARCH 2: VERZENIO in Combination with Fulvestrant

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

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2. (…) VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

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

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months. (…) 14 CLINICAL STUDIES

VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) (MONARCH 3)

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3 was a randomized (2:1), double-blinded, placebo-controlled, multicenter study in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer. (…) VERZENIO in Combination with Fulvestrant (MONARCH 2)

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

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with endocrine therapy who had not received chemotherapy in the metastatic setting. (…) VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

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

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. (…) 1 INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

• for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting.

6 ADVERSE REACTIONS

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

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

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

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| 125427, 05/03/2019                     | Ado-Trastuzumab Emtansine | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies | 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 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 260 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months. (…)

14 CLINICAL STUDIES:

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

VERZENIO in Combination with Fulvestrant (MONARCH 2): Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy. MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. (…)

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1): Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting. MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. (…)

1 INDICATIONS AND USAGE:

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

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

2 DOSAGE AND ADMINISTRATION:

2.1 Patient Selection: Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1), Clinical Studies (14)]. Assessment of HER2 protein overexpression and/or HER2 gene amplification should be performed using FDA-approved tests specific for breast cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

3 ADVERSE REACTIONS:

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the WARNINGS AND PRECAUTIONS reflect exposure to KADCYLA as a single agent at 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) in 1624 patients including 884 patients with HER2-positive metastatic breast cancer and 740 patients with HER2-positive early breast cancer (KATHERINE trial).

Metastatic Breast Cancer: In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. The most common (≥ 25%) adverse reactions were fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation and epistaxis.

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| 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 EMLILA trial [see Clinical Studies (14.1)]. Patients were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.5 months for patients treated with lapatinib and capecitabine, respectively. (…) Early Breast Cancer KADCYLA has been evaluated as a single-agent in 740 patients with HER2-positive early breast cancer. The adverse reactions described in Table 5 were identified in patients with HER2-positive early breast cancer treated in the KATHERINE trial [see Clinical Studies (14.2)]. Patients were randomized to receive KADCYLA or trastuzumab. The median duration of study treatment was 10 months for patients in the KADCYLA-treated group and 10 months for patients treated with trastuzumab. (…) 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Cardiac Electrophysiology The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open-label, single-arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., > 20 ms) were detected in the study. 12.3 Pharmacokinetics Effect of Hepatic Impairment The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=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 radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory using Ventana’s PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent(s)), and pathological nodal status evaluation after preoperative therapy. KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. (…) The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 94% of these patients received pertuzumab. (…) 14.3 HER2-Positive, Metastatic NSCLC 1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see Clinical Pharmacology (12.1) and Clinical Studies (14.1)]. Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations [see Clinical Studies (14.1)]. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC 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/CompanionDiagnosics. 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

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<td>208434, 06/05/2018</td>
<td>Alectinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>(…) The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naive, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650], LUX-Lung 4 [NCT00094650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic therascreen® EGFR RQG PCR Kit, which is FDA-approved for selection of patients for GILOTRIF treatment. Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations. Pre-specified exploratory subgroup analyses were conducted according to the stratification factor of EGFR mutation category. See Figure 2 and text below Figure 2. Overall Response Rate In Other EGFR Mutations The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions was evaluated in a pooled analysis of such patients enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148], LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT01121393]). • LUX-Lung 2 was a single arm, multicenter study of alectinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue. • LUX-Lung 3 was a randomized, multicenter study comparing treatment with alectinib 40 mg orally once daily to intravenous cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit. • LUX-Lung 6 was a randomized, multicenter study comparing treatment with alectinib 40 mg to intravenous gemcitabine 1000 mg/m2 on day 1 and day 8 plus cisplatin 75 mg/m2 on day 1 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR Kit. Among the 75 GILOTRIF treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. Among the 32 patients with a confirmed non-resistant EGFR mutation; the median age was 60.5 years (range 32-79); 65% 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 no prior systemic therapy for advanced or metastatic disease. The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.</td>
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<td>Alpelisib (1)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>Alectinib reached maximal concentrations at 4 hours following administration of ALECENSA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC. (…) Distribution The apparent volume of distribution is 4.016 L for alectinib and 10.093 L for M4. Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration. Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma. (…) Elimination The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC. 14 CLINICAL STUDIES Previously Untreated ALK-Positive Metastatic NSCLC The efficacy of ALECENSA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ALEX: NCT02075840). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. (…) ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials: NP28761 (NCT01588028) and NP28673 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. (…)</td>
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<td>212526, 05/24/2019</td>
<td>Alpelisib (2)</td>
<td>Oncology</td>
<td>ESRBC (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. 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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 6 ADVERSE REACTIONS 6.1 Clinical Trial Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)]. (…) 14 CLINICAL STUDIES SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)]. (…)</td>
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<th>Therapeutic Area</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text†</th>
</tr>
</thead>
</table>
| 209321, 05/06/2019                      | Amifampridine | Neurology       | NAT2       | Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION 2.5 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers The recommended starting dosage of RUZURGI in pediatric patients weighing 45 kg or more who are known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily taken orally in divided doses. The recommended starting dosage in pediatric patients weighing less than 45 kg who are known NAT2 poor metabolizers is 7.5 mg daily taken orally in divided doses [see Dosage and Administration (2.1), Use in Specific Populations (8.6), 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  

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<tr>
<td></td>
<td><strong>208078, 11/28/2018</strong></td>
<td>Amifampridine</td>
<td>Neurology</td>
<td>NAT2</td>
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<tr>
<td></td>
<td>Phosphate</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td><strong>2 DOSAGE AND ADMINISTRATION</strong></td>
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<td></td>
<td><strong>2.4 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers</strong></td>
<td>The recommended starting dosage of FIRDAPSE in known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily, taken orally in 3 divided doses [see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3, 12.5)].</td>
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<td><strong>8 USE IN SPECIFIC POPULATIONS</strong></td>
<td>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.</td>
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<td></td>
<td><strong>8.8 NAT2 Poor Metabolizers</strong></td>
<td>The effect of FIRDAPSE on QTc interval prolongation was studied in a double-blind, randomized, placebo- and positive-controlled study in 52 healthy individuals (including 23 subjects with poor metabolizer phenotype). Study participants were administered 120 mg FIRDAPSE in 4 equal doses of 30 mg at 4-hour intervals (Dose 1, 2, 3, and 4)[see Clinical Pharmacology (12.5)]. FIRDAPSE did not prolong the QTc interval to any clinically relevant extent. In vitro, FIRDAPSE did not inhibit the human ether-a-go-go-related gene ion channel. 12.5 Pharmacogenomics. Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of FIRDAPSE metabolism. Poor metabolizers, also referred to as &quot;slow acetylators&quot; (i.e., carriers of two reduced function alleles) had higher average plasma amifampridine concentrations than intermediate metabolizers, also referred to as &quot;intermediate acetylators&quot; (i.e., carriers of one reduced and one normal function alleles), and normal metabolizers, also referred to as &quot;fast/rapid acetylators&quot; (i.e., carriers of two normal function alleles). In the TQT study (see Clinical Pharmacology (12.2)), poor metabolizers (N=19) had 1.1 to 3.7 times higher AUC0-4h and 1.3 to 3.7 times higher Cmax than intermediate metabolizers (N=21), 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).</td>
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<td><strong>085971, 07/17/2014</strong></td>
<td>Amitriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
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<td><strong>PRECAUTIONS</strong></td>
<td>Drugs Metabolized by P450 2D6</td>
<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 &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. (…)</td>
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<tbody>
<tr>
<td>204325, 09/15/2017</td>
<td>Amphetamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMAOCOLOGY 12.3 Pharmacokinetics Elimination Metabolism and Excretion Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form α-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.</td>
</tr>
</tbody>
</table>
| 020541, 12/13/2018                     | Anastrozole | Oncology   | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies | 14.3 Second-Line Therapy in Postmenopausal Women with Advanced Breast Cancer who had Disease Progression following Tamoxifen Therapy | * Therapeutic areas do not necessarily reflect the CDER review division.
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<td>02/23/2017</td>
<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylarformoterol is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP3A4. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.</td>
</tr>
<tr>
<td>05/29/2019</td>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylarformoterol is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP3A4. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.</td>
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<tr>
<td>02/23/2017</td>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inhibitors (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response. (See Table 2)</td>
</tr>
</tbody>
</table>
| 11/30/2018                            | Aripiprazole Lauroxil | Psychiatry | CYP2D6 | 2 DOSAGE AND ADMINISTRATION | 2.4 Dose Adjustments for Cytochrome P450 Considerations

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors. (…) Studies in Specific Populations

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In pediatric patients (10 to 17 years of age) administered with Abilify (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults. (See Figure 4 and 5) |

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<td>021248, 06/20/2019</td>
<td>Arsenic Trioxide</td>
<td>Oncology</td>
<td>PML-RARA</td>
<td>Indications and Usage, Clinical Studies</td>
<td>(…) Elimination of aripiprazole is mainly through hepatic metabolism involving CYP 3A4 and CYP 2D6. Dosage adjustments are recommended in CYP 2D6 poor metabolizers due to high aripiprazole concentrations [see Dosage and Administration (2.4)]. (…) Drug Interaction Studies: No specific drug interaction studies have been performed with ARISTADA. The drug interaction data provided below is obtained from studies with oral aripiprazole. Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cm ax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP 2D6 and CYP 3A4 inhibitors. After oral administration, a 3-fold increase in mean Cm ax and AUC values at steady-state is expected in poor metabolizers of CYP 2D6 administered with strong CYP 3A4 inhibitors. (See Figure 1, 2, and 3) Specific Population Studies: A population pharmacokinetic analysis showed no effect of sex, race or smoking on ARISTADA pharmacokinetics [see Use in Specific Populations (8.3)]. Exposures of aripiprazole and dehydro-aripiprazole using oral aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. (See Figure 4 and 5)</td>
</tr>
<tr>
<td>022466, 11/02/2018</td>
<td>Articaine and Epinephrine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
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<td>Atezolizumab (1)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>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. 1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer: TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with untreated 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 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)].</td>
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<td>Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma or triple-negative breast cancer are available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>Previously Treated Metastatic NSCLC</td>
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<td>(…) The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see Clinical Studies (14.2)]. (…)</td>
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<td>6.2 Immunogenicity</td>
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<td>(…) 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.</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Specific Populations</td>
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<td>Age (21–85 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 60 mL/min/1.73 m²), mild hepatic impairment (bilirubin ≤ ULN and AST &gt; ULN or bilirubin &lt; 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. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.1 Urothelial Carcinoma</td>
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<td>Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma</td>
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<td>(…) 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 &lt; 5% (PD-L1 stained tumor infiltrating IC covering &lt; 5% of the tumor area).</td>
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<td>Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 87 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an ECOG PS of 2, 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.</td>
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<td>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) (…)</td>
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<td>(…) Both cisplatin-eligible and cisplatin-ineligible patients are included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The independent Data Monitoring Committee (IDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of &lt;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.</td>
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<td>(…) 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 &lt;5%</td>
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<td>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: 831 12.3%, 34.7%). (See Table 15) (…)</td>
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<td>14.2 Non-Small Cell Lung Cancer</td>
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<td>Metastatic Chemotherapy-Naive Non-Squamous NSCLC</td>
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<td>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 tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.</td>
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<td>The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the IGE-WT (patients with high expression of T-effector gene signature [IGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the IGE-WT subpopulation, and ORR/DoR in the IGE-WT and ITT-WT subpopulations.</td>
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<td>Among the 32 patients with PD-L1 expression of ≥ 5%:</td>
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<td>Eight percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.</td>
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<td>Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 78 years, 80% were male, 20% 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.</td>
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A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the IGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 65 years (range: 31 to 85 years), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m² while the remaining 87% received paclitaxel at a dose of 200 mg/m². Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 76%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC.

The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the IGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 16 and Figure 1. (…) Previous Treated Metastatic NSCLC

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

Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m² intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 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]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v1.1. Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors. (See Table 17 and Figure 2).

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression status for prespecified analyses of the 850 patients. 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.62 (95% CI: 0.48, 0.96) in patients who did not have high PD-L1 expression. 14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

Patients with locally advanced or metastatic triple-negative breast cancer whose disease progressed during or following a taxane or anthracycline-containing regimen. The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (2:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (TGE) status and ECOG performance status 0 or 1. (…) Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated 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 major efficacy outcome measures were progression free survival (PFS) by RECIST v1.1 in the IGE-WT (patients with high expression of T-effector gene signature [TGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the IGE-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the IGE-WT subpopulation. OS in the IGE-WT subpopulation, and ORR/DoR in the IGE-WT and ITT-WT subpopulations.

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the IGE-WT subpopulation. (…) * Therapeutic areas do not necessarily reflect the CDER review division.
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| 761034, 05/06/2019                     | Atezolizumab (3) | Oncology | EGFR | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Non-Small Cell Lung Cancer
• TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations. • TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. |
| 761034, 05/06/2019                     | Atezolizumab (4) | Oncology | ALK | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
1.2 Non-Small Cell Lung Cancer
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| 021411, 05/19/2017                    | Atomoxetine | Psychiatry | CYP2D6 | Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
2.4 Dosing in Specific Populations
Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs. In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. |

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#### 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 (11% of PMs, 7% of EMs); feeling jittery (6% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (6% of PMs, 2% of EMs); hyponatremia (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of EMs). (…*)

*Adult Clinical Trials*  
(…*) The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: vision blurred (4% of PMs, 1% of EMs); dry mouth (35% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs); feeling jittery (6% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (6% of PMs, 2% of EMs); hyponatremia (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 Cmax is about 3- to 4-fold greater than atomoxetine alone. In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

**8 USE IN SPECIFIC POPULATIONS**

**8.6 Hepatic Insufficiency**

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

**8.8 Ethnic Origin**

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

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

Cardiac Electrophysiology  
The effect of STRATTERA on QTc prolongation was evaluated in a randomized, double-blind, 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. (…*)

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<td>021881, 12/07/2018</td>
<td>Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>Since MovPrep contains sodium ascorbate and ascorbic acid, MovPrep should be used with caution in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, especially G-6-PD deficiency patients with an active infection, with a history of hemolytic anemia, or taking concomitant medications known to precipitate hemolytic reactions.</td>
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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (1)</td>
<td>Hematology</td>
<td>F2 (Prothrombin)</td>
<td>Warnings and Precautions</td>
<td>DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) 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.</td>
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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (2)</td>
<td>Hematology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and 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.</td>
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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (3)</td>
<td>Hematology</td>
<td>PROC</td>
<td>Warnings and Precautions</td>
<td>DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and 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.</td>
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<tr>
<td>210238, 06/30/2019</td>
<td>Avatrombopag (4)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
<td>DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) 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.</td>
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<sup‡</sup> Referenced figures and tables may be found in the labeling available at Drugs@FDA.

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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
</tr>
</thead>
</table>
| 06/30/2019 | 210238, 761049, 210238 | Avatrombopag | Hematology | SERPINC1 (Antithrombin III) | Warnings and Precautions | **5 WARNINGS AND PRECAUTIONS**  
5.1 Thrombotic/Thromboembolic Complications  
DOPTETEL 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 a treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTETEL 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). DOPTETEL should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 06/30/2019 | 210238 | Avatrombopag | 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]). |
| 12/20/2018 | 016324 | Azathioprine | Rheumatology | TPMT | Dosage and Administration | **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, CYTOTOXIC EFFECTS, ADVERSE REACTIONS, Clinical Pharmacology, 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). |

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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</thead>
</table>
| 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
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, 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, PRECAUTIONS: Laboratory Tests). 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). 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).

PRECAUTIONS

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

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

(…) 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 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. (…)

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</table>
| 206256, 04/12/2017                    | Belinostat    | Oncology          | UGT1A1     | Dosage and Administration, Clinical Pharmacology | 2.3 Patients with Reduced UGT1A1 Activity  
Reduce the starting dose of Beleodaq to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele [see Clinical Pharmacology (12.5)]. |
| 210498, 01/23/2019                    | Binimetinib   | 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)]. |

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| UGT1A1     | TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the +2 and +3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed.  
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 20% of the black population, 10% of the white population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele. Additional reduced function alleles may be more prevalent in specific populations.  
Because belinostat is primarily (80-90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (e.g., patients with UGT1A1*28 allele). Reduce the starting dose of Beleodaq to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities.  
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)].  
| BRAF       | 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)].  
|            | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacogenomics  
BRAF mutation-positive melanoma: In patients with BRAF mutation-positive melanoma, PK of MEKTOVI and encorafenib was dose-proportional, consistent with linear PK. The PK of encorafenib decreased at doses ≥ 300 mg once daily. The PK of dabrafenib decreased at doses ≥ 300 mg once daily.  
|            | 12.5 Pharmacogenomics  
BRAF mutation-positive melanoma: In patients with BRAF mutation-positive melanoma, PK of MEKTOVI and encorafenib was dose-proportional, consistent with linear PK. The PK of encorafenib decreased at doses ≥ 300 mg once daily. The PK of dabrafenib decreased at doses ≥ 300 mg once daily. |

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<td>210498, 01/23/2019</td>
<td>Binimetinib (2)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Drug Interaction Studies Clinical Studies Effect of UGT1A1 Inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Simulations predict similar Cmax of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).</td>
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</table>
| 125557, 04/18/2019                    | Blinatumomab | Oncology | BCR-ABL1 (Philadelphia chromosome) | Adverse Reactions, Clinical Studies | 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL The safety data described below reflect exposure to BLINCYTO in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO (n = 287) or standard of care (SOC) chemotherapy (n = 109). (…)
14.2 Relapsed/Refractory B-cell Precursor ALL TOWER Study. The efficacy of BLINCYTO was compared to standard of care (SOC) chemotherapy in a randomized, open-label, multicenter study (TOWER Study). (…)
| 202258, 01/30/2017                  | Boceprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology | 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 and Ribavirin (PR). IL28B rs12979860 was genotyped in 653 of 1048 (62%) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPOND-2 (previously partial responders and relapers) [see Clinical Studies (14) for trial descriptions]. Among patients who 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 Peginteron and REBETOL (see Table 9). Among previous treatment failures, subjects of all genotypes appeared to have higher SVR rates with regimens containing VICTRELIS. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the substudy population relative to the overall trial population. (See Table 9) |
| 203341, 10/18/2018                  | Bosutinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE BOSULIF is indicated for the treatment of adult patients with: Newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial. Chronic phase, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy. 2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosing The recommended dose is taken orally once daily with food. The tablet is to be swallowed whole and should not be broken or cut. Continue treatment with BOSULIF until disease progression or intolerance to therapy.
If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual prescribed dose on the following day. 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. 2.5 Dose Adjustments for Renal Impairment or Hepatic Impairment |

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<td>Brentuximab Vedotin (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Clinical Studies</td>
<td>The recommended starting doses for patients with renal and hepatic impairment are described in Table 2 below. (See Table 2)</td>
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<tr>
<td>125388, 11/16/2018</td>
<td>Brentuximab Vedotin (2)</td>
<td>Oncology</td>
<td>TNFRSF8 (CD30)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Systemic Anaplastic Large Cell Lymphoma Clinical Trial in Relapsed sALCL (Study 2) (…) The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative. (…)</td>
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<td>Brexpiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>2.1 Recommended Dosage</td>
<td>For dosing instructions of combination agents administered with ADCETRIS, see Clinical Studies (14.1 and 14.2) and the manufacturer’s prescribing information. (See Table 1)</td>
</tr>
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</table>

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

(…) Data summarizing ADCETRIS exposure are also provided for 347 patients with T-cell lymphoma, including 223 patients with PTCL who received ADCETRIS in combination with chemotherapy in a randomized, double-blind, controlled trial; 58 patients with sALCL who received ADCETRIS monotherapy in a single-arm trial; and 66 patients with pcALCL or CD30-expressing MF who received ADCETRIS monotherapy in a randomized, controlled trial. (…) Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30- Expressing Peripheral T-Cell Lymphomas (Study 6, ECHELON-2)
ADCETRIS in combination with CHP was evaluated in patients with previously untreated, CD30- expressing PTCL in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. (See Table 7) (…) Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides (Study 4: ALCANZA)
ADCETRIS was studied in 131 patients with pcALCL or CD30-expressing MF requiring systemic therapy in a randomized, open-label, multicenter clinical trial in which the recommended starting dose and schedule was ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician’s choice of either melphalan 5 to 50 mg orally weekly or bexarotene 300 mg/m2 orally daily. (See Table 9) (…) 

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

14 CLINICAL STUDIES

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

Randomized Clinical Trial in Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6: ECHELON-2, NCT01777152)
The efficacy of ADCETRIS in combination with chemotherapy for the treatment of adult patients with previously untreated, CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. For enrollment, the trial required CD30 expression ≥10% per immunohistochemistry. The trial excluded patients with primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. (See Table 13) (…) 

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

Randomized Clinical Trial in Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA, NCT01578499)
The efficacy of ADCETRIS in patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) requiring systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. (…) Patients with pcALCL must have received prior radiation or systemic therapy, and must have had ≤1 biopsy with CD30 expression of ≥10%. Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30 expression of ≥10% in at least 1 biopsy. 

A total of 131 patients were randomized (66 ADCETRIS, 65 physician’s choice). The efficacy results were based on 128 patients (64 patients in each arm with CD30 expression of ≥10% in at least one biopsy). (See Table 15) (…) Supportive trials include 2 single-arm trials, which enrolled patients with MF who were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Out of 73 patients with MF from the 2 pooled supportive trials, 34% (25/73) achieved ORR4. Among these 73 patients, 35 had 1% to 9% CD30-expression and 31% (11/35) achieved ORR4. 

205422, 02/09/2018

Brexipiprazole

Psychiatry

CYP2D6

Dosage and Administration, Use in Specific Populations, Clinical Pharmacology

2 2.3 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inhibitors or Inducers

Dose adjustment 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) 

8 USE IN SPECIFIC POPULATIONS

8.6 CYP2D6 Poor Metabolizers

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

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug Interaction Studies

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<tr>
<td>208772, 12/21/2018</td>
<td>Brigatinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-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>
</tr>
<tr>
<td>205836, 05/12/2018</td>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.</td>
</tr>
<tr>
<td>009386, 12/24/2003</td>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (…) Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph) chromosome. Also, the so-called “juvenile” type of chronic myelogenous leukemia, typically occurring in young children and associated with the absence of a Philadelphia chromosome, responds poorly to busulfan. The drug is of no benefit in patients whose chronic myelogenous leukemia has entered a “blastic” phase. (…)</td>
</tr>
<tr>
<td>203756, 01/12/2018</td>
<td>Cabozantinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (…) Of 330 patients randomized, 67% were male, the median age was 55 years, 23% were 65 years or older, 89% were white, 54% had a baseline ECOG performance status of 0, and 62% 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>208966, 02/22/2019</td>
<td>Capcitabine</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Dihydropyrimidine Dehydrogenase Deficiency 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 XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA. Withholding or permanently discontinue XELODA based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No XELODA dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.</td>
</tr>
<tr>
<td>016608, 03/20/2018</td>
<td>Carbamazepine (1)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>BOXED WARNING Serious dermatologic reactions and HLA-B<em>1502 allele Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B</em>1502, an inherited atelic variant of the HLA-B gene. HLA-B<em>1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B</em>1502 prior to</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling

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<tr>
<td>016608, 03/20/2018</td>
<td>Carbamazepine (2)</td>
<td>Neurology</td>
<td>HLA-A</td>
<td>Warnings</td>
<td>Serious Dermatologic Reactions</td>
</tr>
<tr>
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<td></td>
<td>Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Tegretol should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.</td>
</tr>
<tr>
<td>02562, 11/16/2017</td>
<td>Carglumic Acid</td>
<td>Inborn Errors of Metabolism</td>
<td>NAGS</td>
<td>1 INDICATIONS AND USAGE</td>
<td>1.1 Acute hyperammonemia in patients with NAGS deficiency</td>
</tr>
<tr>
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<td>Carbagil is indicated as an adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During acute hyperammonemic episodes concomitant administration of Carbagil with other ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction are recommended.</td>
</tr>
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<td>204370, 05/24/2019</td>
<td>Cariprazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td></td>
<td>12.3 Pharmacokinetics</td>
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<td>CYP2D6 Poor Metabolizers</td>
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<td>CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.</td>
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<td>Drug Interaction Studies</td>
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<td></td>
<td></td>
<td>CYP2P2D6 inhibitors</td>
</tr>
<tr>
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<td></td>
<td>CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.</td>
</tr>
<tr>
<td>011792, 04/04/2019</td>
<td>Carisoprodol</td>
<td>Rheumatology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.8 Patients with Reduced CYP2C19 Activity</td>
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<td></td>
<td>Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients [see Clinical Pharmacology (12.3)].</td>
</tr>
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<tr>
<td>02/09/2017</td>
<td>010354, 020354</td>
<td>Carvedilol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>Soma should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carisoprodol, and concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.</td>
</tr>
<tr>
<td>02/09/2018</td>
<td>010355, 020355</td>
<td>Celecoxib</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.7 Special Populations Poor Metabolizers of CYP2C9 Substrates In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)].</td>
</tr>
</tbody>
</table>
| 03/03/2018 | 010356, 020356        | Ceftriaxone (1) | Infectious Diseases | G6PD | Warnings | Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 04/03/2018 | 010357, 020357        | Ceftriaxone (2) | Infectious Diseases | Nonspecific (Congenital Methemoglobinemia) | Warnings | Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 03/15/2019 | 010358, 020358        | Ceritinib     | Oncology          | ALK | Indications and Usage, Dosage and Administration | 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. |

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| 761052, 12/11/2018                     | Cerliponase Alfa | Inborn Errors of Metabolism | TPP1      | Indications and Usage, Use in Specific Populations, Clinical Studies | 2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens (see Indications and Usage and Clinical Studies (14.1)). Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics

5 WARNINGS AND PRECAUTIONS
Data in the Warnings and Precautions section reflect the safety of ZYKADIA 750 mg daily under fasted conditions in 925 patients with ALK-positive NSCLC across a pool of seven clinical studies at systemic exposures similar to the recommended dose of 450 mg with food. In a dose optimization study (ASCEND-8), there were no clinically meaningful differences observed in the incidence of toxicities described in Warnings and Precautions between patients receiving 750 mg daily under fasted conditions and 450 mg with food, except for a reduction in gastrointestinal adverse reactions as described (see Warnings and Precautions (5.1)).

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

The data in the Warnings and Precautions section reflect exposure to ZYKADIA 750 mg once daily in 925 patients with ALK-positive NSCLC across seven clinical studies, including ASCEND-4 and ASCEND-1, described below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies. In ASCEND-8, a dose optimization study, ZYKADIA 450 mg daily with food (N = 89) was compared to 750 mg daily under fasted conditions (N = 90) in both previously treated and untreated patients with ALK-positive NSCLC. The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study of 376 previously untreated ALK-positive NSCLC patients. Patients received ZYKADIA 750 mg daily (N=187) or chemotherapy plus maintenance chemotherapy (N=189). The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in ASCEND-1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily). (See Tables 5 and 6)

14 CLINICAL STUDIES
14.1 Previously Untreated ALK-Positive Metastatic NSCLC
The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ASCEND-4, NCT01828359). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (ASCEND-1, NCT01283516). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily, and the study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastases included brain (63%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

14.2 Previously Treated ALK-Positive Metastatic NSCLC
The safety evaluation of ZYKADIA was based on ASCEND-4 and ASCEND-1, described below. In ASCEND-8, a dose optimization study, ZYKADIA 450 mg daily with food (N = 89) was compared to 750 mg daily under fasted conditions (N = 90) in both previously treated and untreated patients with ALK-positive NSCLC. (…)

14 CLINICAL STUDIES
14.3 Pre-treatment ALK-Positive Metastatic NSCLC
The efficacy of ZYKADIA was established in an open-label, randomized, active-controlled, multicenter clinical trial (ASCEND-4, NCT01828359). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily, and the study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastases included brain (63%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

14 CLINICAL STUDIES
14.4 Previously Treated ALK-Positive Metastatic NSCLC
The efficacy of ZYKADIA was established in an open-label, randomized, active-controlled, multicenter clinical trial (ASCEND-4, NCT01828359). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily, and the study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastases included brain (63%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

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<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>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). (…) <strong>Motor Domain Scores: Matched Patients Only</strong> (…) 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>
</tr>
<tr>
<td>125084, 04/23/2019</td>
<td>Cetuximab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions</td>
<td>* Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.</td>
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**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-expressing 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/productsandmedicaldevicesprocedures/invitrodiagnostics/ur_m301431.htm

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

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

In Combination with FOLFIRI

(…) The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…) As Monotherapy

(…) The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) (See Warnings and Precautions (5.8)). ERBITUX was administered intravenously at the recommended dosage (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range 1 to 51) (see Clinical Studies (14.2)). (See Table 5) (…) In Combination with Irinotecan

ERBITUX at the recommended dosage was administered in combination with irinotecan in 354 patients with EGFR expressing recurrent mCRC in Study CP02-9523 and BOND. (…) |

**14 CLINICAL STUDIES**

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

In Combination with FOLFIRI

CRYSTAL (NCT00154102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive 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

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. (…) |
Table of Pharmacogenomic Biomarkers in Drug Labeling
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<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Precautions, Adverse Reactions, Clinical Studies</td>
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<td></td>
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<td>• in combination with inotropes in patients who are refractory to inotrope-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 intolerance to inotrope. [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 he results of the Ras mutation tests are unknown (see Warnings and Precautions (5.7). Clinical Studies (14.2)).</td>
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<td></td>
<td>2 DOSAGE AND ADMINISTRATION</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></td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC</td>
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<td>Erbitux is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as “Ras” or when the Ras status is unknown. Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials including Study 4 were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. (See Indications and Usage (1.2), Clinical Pharmacology (12.1), Clinical Studies (14.2).)</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)</td>
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<td>In Combination with FOLFIRI</td>
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<td>(...) The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…)</td>
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<td></td>
<td>As Monotherapy</td>
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<td>The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) (see Warnings and Precautions (5.8)). (See Table 5) (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)</td>
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<td>In Combination with FOLFIRI</td>
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<td>(...) 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. (…)</td>
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<td>(...) Results of the planned PFS and ORR analysis in all randomized patients and post-hoc PFS and ORR analysis in subgroups of patients defined by K-Ras mutation status, and post-hoc analysis of updated OS based on additional followup (1000 events) in all randomized patients and in subgroups of patients defined by K-Ras mutation status are presented in Table 8 and Figure 2. The treatment effect in the all-randomized population for PFS was driven by treatment effects limited to patients who have K-Ras wild-type tumors. There is no evidence of effectiveness in the subgroup of patients with K-Ras mutant tumors. (See Table 8 and Figure 2) (…)</td>
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<td>(...) 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) (…)</td>
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<td>In Combination with Irinotecan</td>
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<tr>
<td>020969, 12/08/2006</td>
<td>Cevimeline</td>
<td>Dental</td>
<td>CYP2D6</td>
<td>Precautions</td>
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<td>PRECAUTIONS</td>
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<td>(...) Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an in vitro study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline. (…)</td>
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<tr>
<td>006002, 10/24/2018</td>
<td>Chloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
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<td>PRECAUTIONS</td>
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<td>Hematological Effects/Laboratory Tests</td>
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<td>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, discontinuation 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>
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<td>ADVERSE REACTIONS</td>
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<td>Blood and lymphatic system disorders: Pancytopenia, aplastic anemia, reversible granulocytosis, thrombocytopenia and neutropenia. Hemolytic anemia in G6PD deficient patients (see PRECAUTIONS).</td>
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</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>011641, 02/01/2011</td>
<td>Chloropramide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
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<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td></td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chloroprocaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
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</tr>
<tr>
<td>0118057, 02/22/2019</td>
<td>Cisplatin</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Adverse Reactions</td>
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</tr>
<tr>
<td>020922, 01/11/2019</td>
<td>Citalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>DOSAGE AND ADMINISTRATION</td>
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<tr>
<td>020922, 01/11/2019</td>
<td>Citalopram (2)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td></td>
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<tr>
<td>200207, 06/15/2018</td>
<td>Clofazam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers</td>
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</tbody>
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<tbody>
<tr>
<td>019906, 05/10/2019</td>
<td>Clozapine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS&lt;br&gt;Drugs Metabolized by P450 2D6&lt;br&gt;The biochemical activity of the drug metabolizing isomerase cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Dependence 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>020839, 05/17/2019</td>
<td>Clopidogrel</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Boxed Warning, Warnings and Precautions, Clinical Pharmacology</td>
<td>BOXED WARNING&lt;br&gt;DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE&lt;br&gt;The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed &quot;CYP2C19 poor metabolizers&quot;). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.</td>
</tr>
<tr>
<td>019758, 02/23/2017</td>
<td>Clozapine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION&lt;br&gt;2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers&lt;br&gt;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 (8.8, 8.7)].</td>
</tr>
<tr>
<td>208192, 01/20/2016</td>
<td>Cobimetinib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage</td>
<td>1 INDICATIONS AND USAGE</td>
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<tbody>
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<td>022402, 09/18/2018</td>
<td>Codeine</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>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>

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**

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

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

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

**14 CLINICAL STUDIES**

The safety and efficacy of cobimetinib was established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trial conducted in 405 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic melanoma. The presence of BRAF V6000 mutation was detected using the cobas® 4800 BRAF V600 mutation test. (…) The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review. A trend favoring the cobimetinib with vemurafenib arm was observed in exploratory subgroup analyses of PFS, OS, and DRR in both BRAF V600 mutation subtypes (V600E or V600K) in the 81% of patients in this trial where BRAF V600 mutation type was determined.

**5 WARNINGS AND PRECAUTIONS**

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

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

**8 USE IN SPECIFIC POPULATIONS**

**8.2 Lactation**

Risk Summary

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine’s active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed patients. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Codeine Sulfate Tablets and any potential adverse effects on the breastfed infant from Codeine Sulfate Tablets or from the underlying maternal condition.

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<td>202570, 06/25/2019</td>
<td>Crizotinib (1)</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>8.4 Pediatric Use The safety and effectiveness of Codeine Sulfate Tablets in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received codeine [see Warnings and Precautions (5.4)]. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine. (…)**</td>
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<td>06/25/2019</td>
<td>Crizotinib (2)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>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)].</td>
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<td>202806,</td>
<td>05/04/2018</td>
<td>Dabrafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma TAFINLAR is indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)].</td>
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|                                       |      |                   |            |                   | TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.4)].  
1.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer  
TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)].  
1.6 Limitations of Use  
TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC [see Warnings and Precautions (5.2)]. |

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection  
Melanoma  
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent [see Warnings and Precautions (5.2) and Clinical Studies (14.1)].  
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Warnings and Precautions (5.2), Clinical Studies (14.2), (14.3)].  
- Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics-NOSLC.  
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Clinical Studies (14.4)].  
- Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics-NSCLC.  
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Clinical Studies (14.5)].  

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

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.  
The data described in the Warnings and Precautions section reflect exposure to TAFINLAR administered as a single agent in 586 patients with various solid tumors and exposure to TAFINLAR administered with trametinib in 559 patients with melanoma and 93 patients with NSCLC. The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 300 mg).  
Metastatic or Unresectable BRAF V600E Mutation Positive Melanoma  
TAFINLAR as a Single Agent  
Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of the BREAK-3 study [see Clinical Studies (14.1)]. This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m2 intravenously every 3 weeks (n = 63).  
TAFINLAR Administered with Trametinib  
The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with melanoma in 3 trials, Trial 2 (n = 209) a multicenter, double-blind, randomized (1:1), active controlled trial and Trial 3 (n = 350) a multicenter, open-label, randomized (1:1), active controlled trial.  
Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma  
The safety of TAFINLAR when administered with trametinib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study [see Clinical Studies (14.3)].  
Metastatic, BRAF V600E-Mutation Positive, Non-Small Cell Lung Cancer (NSCLC)  
The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, non-randomized, open-label trial (Study BRF113928).  
Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC)  
The safety of TAFINLAR when administered with trametinib, non-randomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). |

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

14 CLINICAL STUDIES
14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent
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. (…)

14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR Administered with Trametinib
The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908).

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 THxID™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or TAFINLAR 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)
In Study BRF113928 (NCT01366334), the safety and efficacy of TAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity estimating, nine-cohort, cohort multicenter trial. (See Table 12) (…)

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 samples from 243 patients (97%) were tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF assay (…).

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| 202808, 05/04/2018                     | Dabrafenib (2) | Oncology | G6PD | Warnings and Precautions, Adverse Reactions, Patient Counseling Information | 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. |
| 202808, 05/04/2018                     | Dabrafenib (3) | Oncology | RAS | Dosage and Administration, Warnings and Precautions | 2 DOSAGE AND ADMINISTRATION
2.3 Dose Modifications
For New Primary Non-Cutaneous Malignancies
Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies. |
| 206843, 11/09/2017                     | Daclatasvir | Infectious Diseases | IFNL3 (IL28B) | 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; 50% 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 NSSA amino acid polymorphisms, see Microbiology (12.4). (…) |

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<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>(…) SVR12 rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level. For SVR12 outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…)</td>
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</table>
| 09/27/2018                             | Dapsonel (1) | Dermatology       | G6PD       | Warnings and Precautions, Use in Specific Populations, Patient Counseling Information | 5 WARNINGS AND PRECAUTIONS
5.2 Hematologic Effects
- Oral dapsonel treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.
- Some subjects with G6PD deficiency using ACZONE® Gel developed laboratory changes suggestive of hemolysis. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel. 5%, including patients who were G6PD deficient.
- Discontinue ACZONE® Gel. 5%, if signs and symptoms suggestive of hemolytic anemia occur. Avoid use of ACZONE® Gel. 5% in patients who are taking oral dapsonel 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. |
| 021794, 05/18/2018                     | Dapsonel (1) | Dermatology       | G6PD       | 5 WARNINGS AND PRECAUTIONS
5.2 Hematologic Effects
- Oral dapsonel treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.
- Some subjects with G6PD deficiency using ACZONE® Gel developed laboratory changes suggestive of hemolysis. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel. 5%, including patients who were G6PD deficient.
- Discontinue ACZONE® Gel. 5%, if signs and symptoms suggestive of hemolytic anemia occur. Avoid use of ACZONE® Gel. 5% in patients who are taking oral dapsonel 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>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions, Adverse Reactions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Methemoglobinemia</td>
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<td>Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE® Gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of ACZONE® Gel, 5% in those patients with congenital or idiopathic methemoglobinemia. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in, e.g., buccal mucous membranes, lips and nail beds. Advise patients to discontinue ACZONE® Gel, 5% and seek immediate medical attention in the event of cyanosis. Dapsone can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents.</td>
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#### 14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis

Subjects with Chronic HCV GT1a Infection without Cirrhosis

| Subjects with HCV GT1a infection without cirrhosis treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV [see Clinical Studies (14.1)] had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 95% were White; 5% 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

| Subjects with HCV GT1b infection without cirrhosis treated with VIEKIRA PAK with or without RBV for 12 weeks in PEARL-II and -III [see Clinical Studies (14.1)]. Subjects had a median age of 52 years (range: 22 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were Hispanic or Latino; 21% had a body mass index of at least 30 kg per m²; 21% of patients were enrolled in US sites; 83% had IL28B (rs12979860) non-CC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per mL. (…)

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

| 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; 31% had HCV GT1b infection; 42% were treatment-naïve; 36% had prior pegIFN/RBV null responders; 6% 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

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

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

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

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<td>2.1 Dosage of SPRYCEL in Adult Patients</td>
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<td>The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed: they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.</td>
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<td>2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL</td>
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<td>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. <em>(See Table 1)</em></td>
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<td>Refer to Section 2.4 for recommendations on dose escalation in adults in CML and Ph+ ALL, and pediatric patients with CML.</td>
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<td>2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML</td>
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<td>For adults with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily <em>(see Table 2)</em>. Dose escalation is not recommended for pediatric patients with Ph+ ALL, where SPRYCEL is administered in combination with chemotherapy. Escalates 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. <em>(See Tables 2, 3, and 4)</em></td>
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<td>2.5 Dose Adjustment for Adverse Reactions</td>
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<td>Myelosuppression</td>
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<td>*(…) 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</td>
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<td>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 &gt;3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade 1.&lt;(…)</td>
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<td>2.6 Duration of Treatment</td>
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<td>In clinical studies, treatment with SPRYCEL in adults and in pediatric patients with chronic phase CML was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response (CCyR)) or major molecular response (MMR and MR4.5) has not been established.</td>
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<td>In clinical studies, treatment with SPRYCEL in pediatric patients with Ph+ ALL was administered for a maximum duration of 2 years <em>(see Dosage and Administration (2.2) and Clinical Studies (14.4)</em>. SPRYCEL is an antineoplastic product.</td>
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<td>Follow applicable special handling and disposal procedures.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td></td>
<td>5.1 Myelosuppression</td>
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<td>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.</td>
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<td>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. *(…)</td>
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<td>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. *(…)</td>
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<td>5.2 Bleeding-Related Events</td>
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<td>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 &lt;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.</td>
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<td>5.3 Fluid Retention</td>
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<td>*(…) In patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose <em>(n=304)</em>, grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural effusion reported in 7% of patients. *(…)</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>*(…) The data described below reflect exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and in 2388 patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2712 SPRYCEL-treated patients was 19.2 months (range 0–93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1818 patients with chronic phase CML was 29 months (range 0–92.9 months). The median duration of therapy in 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months). *(…)</td>
</tr>
</tbody>
</table>
|                                        |      |                 |            |                  | *(…) In the randomized trial in patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 36%. Among the 1618 patients treated patients with chronic phase CML and in 2388 patients with imatinib-resistant or -intolerant chronic or advanced 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. Referenced figures and tables may be found in the labeling available at Drugs@FDA. *Therapeutic areas do not necessarily reflect the CDER review division. †Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term ‘Nonspecific’ is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. ‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version."
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<td>SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation were reported in 329 (20.3%) patients; among the 1094 SPRYCEL treated patients with advanced phase CML or Ph+ ALL, drug-related adverse events leading to discontinuation were reported in 191 (17.5%) patients. (…) Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults A total of 135 patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. (…) Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients The safety of SPRYCEL administered continuously in combination with multagent chemotherapy was determined in a 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%–&lt;10%, 0.1%–&lt;1%, or &lt;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 (…) BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L, and V299L. Dasatinib does not appear to be active against the T315I mutation, based on in vitro data. 14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib. 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a pooled analysis of these data, treatment with SPRYCEL was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months); or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases); cytogenetic response, or hematologic response. (…) The primary efficacy endpoint in chronic phase CML was MCyR or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase CML, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL). Advanced Phase CML, and Ph+ ALL Dose-Optimization Trial: One randomized open-label trial was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. (See Table 19). (…) (…) In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The median of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg bidtwice daily were 4.0 months (min-max: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively. 14.4 Ph+ ALL in Pediatric Patients The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a single cohort (cohort 1) of Study CA180372 (NCT01469160), a multicenter, multiple-cohort study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. The 78 patients in cohort 1 received SPRYCEL at a daily dose of 60 mg/m2 for up to 24 months, in combination with chemotherapy. The backbone chemotherapy regimen was the AIEOP-BFM ALL 2000 multi-agent chemotherapy protocol. (…)</td>
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<tr>
<td>103767, 02/15/2019</td>
<td>Denileukin Diftitox</td>
<td>Oncology</td>
<td>IL2RA (CD25 antigen)</td>
<td>Indications and Usage, Warnings and Precautions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE Ontak is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the II-2 receptor [see Warnings and Precautions (5.4)].</td>
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</table>
| 014399, 11/09/2018                    | Desipramine | Psychiatry | CYP2D6 | Precautions | 5.4 CD25 Tumor Expression and Evaluation
Confirm that the patient’s malignant cells express CD25 prior to administration of Ontak. A testing service for the assay of CD25 expression in tumor biopsy samples is available. |
| 020118, 03/01/2019                    | Desflurane | Anesthesiology | Nonspecific (Genetic Susceptibility to Malignant Hyperthermia) | Contraindications | 4 CONTRAINDICATIONS
The use of SUPRANE is contraindicated in the following conditions:
- Known or suspected genetic susceptibility to malignant hyperthermia. (…) |
| 021992, 02/06/2018                    | Desvenlafaxine | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism and elimination
Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. (…) |
| 208082, 06/06/2018                    | Deutetrabenazine | Neurology | CYP2D6 | Dosage and Administration | 2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers
In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Use in Specific Populations (8.7)]. |

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</table>
| 022287, 06/07/2018                     | Dextansoprazole | 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 PHARMACOLOGY
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). Dextansoprazole 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 dextansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dextansoprazole sulfone is the major plasma metabolite.

Cytchrome P 450 Interactions
(…) Although in vitro studies indicated that DEXILANT has the potential to inhibit CYP2C19 in vivo, 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 coadministered compared to administration of clopidogrel alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mM 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 Dextansoprazole
Systemic exposure of dextansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of DEXILANT 30 mg or 60 mg capsules (n=2 to 6 subjects/group), mean dextansoprazole 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 dextansoprazole 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 in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited (see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)). Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 (see Drug Interactions (7.5)).

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

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluate in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 0.8 ms for dextromethorphan 30 mg/quinidine, 1.9 ms for 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 30mg/quinidine 30mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours. (…) Dextromethorphan
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)).

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<tr>
<td>Diazepam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination (...) The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are &quot;poor metabolizers&quot;) and CYP3A4. (...)</td>
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<tr>
<td>Dinutuximab</td>
<td>Oncology</td>
<td>MYCN</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (...) Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 10% of patients. (...)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Adjuvant Treatment of Breast Cancer (...) Docetaxel was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC. (See Table 14) (...)</td>
</tr>
<tr>
<td>Dolugravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1(n = 7) genotypes conferring poor dolugravir metabolism had a 32% lower clearance of dolugravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1(n = 41).</td>
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<tr>
<td>Donepezil</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Poor Metabolizers of CYPs 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.</td>
</tr>
<tr>
<td>Doxepin (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5. Special Population Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
<tr>
<td>Doxepin (2)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5. Special Population Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Gastroenterology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.6 Effect of CYP2C9 Polymorphism Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function (see Clinical Pharmacology (12.5)).</td>
</tr>
<tr>
<td>Drospirenone and Ethinyl Estradiol</td>
<td>Gynecology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Effects of Combined Oral Contraceptives on Other Drugs (...) In the study with 24 postmenopausal women [including 12 women with homoyzogous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. (...)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS 7.3 Dual Inhibition of CYP1A2 and CYP2D6 Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.</td>
</tr>
</tbody>
</table>

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 761069, 02/16/2018                      | 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 85 mL/min), moderate renal impairment (CLCR 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status had no clinically significant effect on the pharmacokinetics of durvalumab. (…)

14 CLINICAL STUDIES
14.1 Urothelial Carcinoma
(…) Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and immune cells (IC) at a central laboratory using the VENTANA PD-L1 (SP263) Assay. Of the 182 patients, 95 were classified as PD-L1 high if ICs involve >1% of the tumor area, TC ≥25% or IC ≥25%; if ICs involve ≥1% of the tumor area, TC ≥25% or IC=100%, 73 as PD-L1 low/negative (did not meet criterion for PD-L1 high), and samples for 14 patients were not evaluable. (see Table B) (…)

| 211155, 09/24/2018                      | Duvelisib | Oncology | Chromosome 17p | Clinical Studies | 14 CLINICAL STUDIES
14.1 Efficacy in Relapsed or Refractory CLL/SLL
Study 1
(…) In this subset (95 randomized to COPIKTRA, 101 to flutamumab), 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. (…)

| 020972, 10/10/2017                      | Efavirenz | Infectious Diseases | CYP2B6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of SUSTIVA on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.5-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 95% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days (see Warnings and Precautions (5.2)).

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

| 208261, 06/26/2018                      | Elbasvir and Grazoprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14 CLINICAL STUDIES
14.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TE and C-EDGE COINFECTION)
(…) C-EDGE TE was a randomized, double-blind, placebo-controlled trial in treatment-naive subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized in a 2:1 ratio to: ZEPATIER for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with ZEPATIER for 12 weeks (deferred treatment group). Among subjects with genotype 1 infection randomized to the immediate treatment group, the median age was 55 years (range: 20 to 78); 56% of the subjects were male; 61% were White; 20% were Black or African American; 8% were Hispanic or Latino; mean body mass index was 26 kg/m²; 72% had baseline HCV RNA levels greater than 800,000 IU/mL; 24% had cirrhosis; 67% had non-C/C IL28B alleles (CT or TT); and 55% had genotype 1a and 45% had genotype 1b chronic HCV infection. C-EDGE COINFECTION was an open-label, single-arm trial in treatment-naive HCV/HIV-1 coinfected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks. Among subjects with genotype 1 infection, the median age was 50 years (range: 21 to 71); 85% of the subjects were male; 75% were White; 19% were Black or African American; 6% were Hispanic or Latino; mean body mass index was 25 kg/m²; 59% had baseline HCV RNA levels greater than 800,000 IU/mL; 16% had cirrhosis; 65% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (…)

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

14.4 Clinical Trials in Treatment-Experienced Subjects who Failed Prior PegIFN + RBV + HCV Protease Inhibitor Therapy (CSALVAGE)
C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects

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<tr>
<td>205494, 08/28/2018</td>
<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>had a median age of 55 years (range: 23 to 75); 58% of the subjects were male; 97% were White; 3% were Black or African American; 15% were Hispanic or Latino; mean body mass index was 28 kg/m²; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; and 97% had non-C/C IL28B alleles (CT or TT); 46% had baseline NS3 resistance-associated substitutions. Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)]. (…) 14.4 Clinical Trial in Subjects with Genotype 1 HCV and Severe Renal Impairment including Subjects on Hemodialysis (C-SURFER) C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m²) or CKD Stage 5 (eGFR&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-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.</td>
</tr>
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<th>Labeling Sections</th>
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</tbody>
</table>

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

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.6 Renal Impairment
Use CERDELGA in patients with renal impairment based on the patient’s CYP2D6 metabolizer status [see Clinical Pharmacology (12.3)].
- **EMs**
  - Avoid CERDELGA in patients with end-stage renal disease (ESRD) (estimated creatinine clearance (eCLcr) less than 15 mL/min not on dialysis or requiring dialysis).
  - No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment (eCLcr at least 15 mL/min).
- **IMs**
  - Avoid CERDELGA in patients with any degree of renal impairment.
- **PMs**
  - Avoid CERDELGA in patients with any degree of renal impairment.

#### 8.7 Hepatic Impairment
Use CERDELGA in patients with hepatic impairment based on CYP2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors [see Clinical Pharmacology (12.3)].
- **EMs**
  - CERDELGA is contraindicated in patients with [see Contraindications (4)]:
    - Severe (Child-Pugh Class C) hepatic impairment
    - Moderate (Child-Pugh Class B) hepatic impairment in patients with mild hepatic impairment taking a strong or moderate CYP2D6 inhibitor
  - Reduce dosage frequency of CERDELGA 84 mg to once daily [see Dosage and Administration (2.3)] in patients with mild hepatic impairment taking: o a strong CYP2D6 inhibitor o a weak CYP3A inhibitor
  - No dosage adjustment is recommended in patients with mild hepatic impairment, unless otherwise specified above.
- **IMs**
  - CERDELGA is contraindicated in patients with any degree of hepatic impairment [see Contraindications (4)].

### 12 CLINICAL PHARMACOLOGY

#### 12.3 Pharmacokinetics
- **Absorption**
  - The oral bioavailability of eliglustat was less than 5% in CYP2D6 EMs following a single 84 mg dose of CERDELGA.
  - In CYP2D6 EMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose-proportional manner over the dose range of 42 to 294 mg (0.5 to 3.5 times the recommended dosage).
  - In addition, after multiple oral doses of 84 mg twice daily in EMs, eliglustat systemic exposure (AUC0-12) increased up to about 2-fold at steady state compared to after the first dose (AUC0-∞). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7-fold to 9-fold higher in PMs.
  - Dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted Cmax and AUC0-24hr in PMs using a physiologically based pharmacokinetic (PBPK) model with 84 mg once daily was 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, race (mostly Caucasian, including those of Ashkenazi Jewish descent; however, it included the following populations: African American, American Indians, Hispanics, and Asians), or body weight (41 to 136 kg).
      - **Patients with renal impairment**
        - Eliglustat pharmacokinetics was similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs. Eliglustat pharmacokinetics in EMs with ESRD and in IMs or PMs with any degree of renal impairment is unknown [see Use in Specific Populations (8.6)].
      - **Patients with hepatic impairment**
        - Eliglustat pharmacokinetics was similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs. Eliglustat pharmacokinetics in EMs with ESRD and in IMs or PMs with any degree of renal impairment is unknown [see Use in Specific Populations (8.6)].

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<td>125460, 02/14/2014</td>
<td>Elosulfase</td>
<td>Inborn Errors of Metabolism</td>
<td>GALNS</td>
<td>Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>Steady-state pharmacokinetics of eliglustat in CYP2D6 IMs and PMs with mild and moderate hepatic impairment is unknown. The effect of severe hepatic impairment in subjects with any CYP2D6 phenotype is unknown [see Use in Specific Populations (8.7)]. Drug Interaction Studies Effect of other drugs on CERDELGA Table 9 describes the effect of drug interactions on the pharmacokinetics of eliglustat [see Drug Interactions (7.1)]. (See Table 9) No clinically significant pharmacokinetic changes were observed for eliglustat when coadministered with intravenous rifampin (an OATP inhibitor), or gastric pH modifying drugs (e.g., aluminum hydroxide, magnesium hydroxide, calcium carbonate, pantoprazole). In vitro, eliglustat is a substrate of P-glycoprotein (P-gp). The effect of P-gp inhibitors on eliglustat pharmacokinetics is unknown. Effect of CERDELGA on other drugs CYP2D6 substrates Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage), metoprolol (a CYP2D6 substrate) mean Cmax and AUC increased by 1.7-fold and 2.3-fold in CYP2D6 EMs, respectively, and by 1.2-fold and 1.6-fold in IMs, respectively [see Drug Interactions (7.2)]. 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 (90%) and URM (5%) patients. (…)</td>
</tr>
<tr>
<td>02/22/91, 11/16/2018</td>
<td>Eltrombopag (1)</td>
<td>Hematology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Risk of Acute Respiratory Complications Patients with acute febrile or respiratory illness at the time of Vimizim infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient’s clinical status prior to administration of Vimizim and consider delaying the Vimizim infusion. Sleep apnea is common in MPS IVA patients. Evaluation of airway patency should be considered prior to initiation of treatment with Vimizim. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an acute reaction, or extreme drowsiness/sleep induced by antihistamine use. 5.3 Spinal or Cervical Cord Compression Spinal or cervical cord compression (SCC) is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease. In clinical trials, SCC was observed both in patients receiving Vimizim and patients receiving placebo. Patients with MPS IVA should be monitored for signs and symptoms of SCC (including back pain, paralysis of limbs below the level of compression, urinary and fecal incontinence) and given appropriate clinical care. 8 USE IN SPECIFIC POPULATIONS Clinical Considerations Disease-associated maternal and embryofetal risk Pregnancy can adversely affect the health of females affected with MPS IVA and lead to adverse pregnancy outcomes for both mother and fetus. 8.3 Nursing Mothers It is not known if Vimizim is present in human milk. Elosulfase alfa is present in milk from treated rats [see Use in Specific Populations (8.1)]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Vimizim and any potential adverse effects on the breastfed child from the drug or from MPS IVA. Exercise caution when administering Vimizim to a nursing mother. There is a Morquio A Registry that also collects data on breastfeeding women with MPS IVA who are treated with Vimizim. 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics The pharmacokinetics of eolosulfase alfa were evaluated in 23 patients with MPS IVA who received intravenous infusions of Vimizim 2 mg/kg once weekly, over approximately 4 hours, for 22 weeks. (…) 14 CLINICAL STUDIES The safety and efficacy of Vimizim were assessed in a 24-week, randomized, double-blind, placebo-controlled clinical trial of 176 patients with MPS IVA. (…)</td>
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<tr>
<td>02/22/91, 11/16/2018</td>
<td>Eltrombopag (2)</td>
<td>Hematology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.3 Thrombotic/Thromboembolic Complications Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). (…)</td>
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<td>Enasidenib</td>
<td>Oncology</td>
<td>IDH2</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: 1.1 Acute Myeloid Leukemia IDHI FA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.</td>
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<td>PRF1, RAB27A, SH3D1A, STXB2, STX11, UNC13D, XAP (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%), FH2-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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</table>

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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). (…)
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<tr>
<td>210496, 05/24/2019</td>
<td>Encorafenib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>BRAFTOVI™ 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)]. Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>017087, 01/21/2010</td>
<td>Enflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Contraindications</td>
<td>CONTRAINDICATIONS (…) Known or suspected genetic susceptibility to malignant hyperthermia.</td>
</tr>
<tr>
<td>212018, 04/12/2019</td>
<td>Erdafitinib (1)</td>
<td>Oncology</td>
<td>FGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies, Patient Counseling Information</td>
<td>1 INDICATIONS AND USAGE BALKIVERSTM is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), that has: • susceptible FGFR3 or FGFR2 genetic alterations, and • progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for BALKIVERSTM (1). 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of locally advanced or metastatic urothelial carcinoma with BALKIVERSTM based on the presence of susceptible FGFR3 genetic alterations in tumor specimens as detected by an FDA-approved companion diagnostic [see Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of FGFR3 genetic alterations in urothelial cancer is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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<td></td>
<td>Eribulin (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>14 CLINICAL STUDIES</td>
<td>14.1 Metastatic Breast Cancer</td>
</tr>
<tr>
<td>201532, 10/19/2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(…) Randomization was stratified by geographic region, HER2/neu status, and prior cetuximab exposure. HALAVEN was administered at a dose of 1.4 mg/m2 on Days 1 and 8 of a 21-day cycle. HALAVEN-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% cetuximab, 16% taxane, 16% 5-fluorouracil, 10% other chemotherapy), 1% hormonal therapy, 1% other systemic therapy, and 1% unknown therapy. The main efficacy outcome was overall survival. (…) (…) Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER-, PR-, HER2/neu-), presence of visceral disease (82%, including 60% liver and 15% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of at least four prior chemotherapy regimens in both arms. (See Table 5) (…)</td>
</tr>
<tr>
<td></td>
<td>Eribulin (2)</td>
<td>Oncology</td>
<td>CYP2C8</td>
<td>12 CLINICAL PHARMACOLOGY</td>
<td>12.5 Pharmacogenomics</td>
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<tr>
<td>201532, 10/19/2016</td>
<td></td>
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<td></td>
<td></td>
<td>CYP2C9 activity is reduced in individuals with genetic variants, such as the CYP2C9<em>2 and CYP2C9</em>3 polymorphisms. Eribulin exposure was similar in subjects with CYP2C9*1/*2 and *1/<em>3 genotypes relative to subjects with CYP2C9</em>1/*1 genotype (wild type). No data are available in subjects characterized by other genotypes (e.g., *2/*2, *2/*3, *3/<em>3). Simulation suggested no clinically meaningful differences in eribulin exposure in subjects with CYP2C9</em>2/*2 and *2/<em>3 genotypes. The exposure of eribulin is predicted to be 50% higher in subjects with the CYP2C9</em>3/*3 genotype, estimated to be present in 0.4% to 3% of the population among various ethnic groups.</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>14 CLINICAL STUDIES</td>
<td>14.1 Metastatic Breast Cancer</td>
</tr>
<tr>
<td>021743, 10/18/2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(…) Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER-, PR-, HER2/neu-), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of at least four prior chemotherapy regimens in both arms. (See Table 5) (…)</td>
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</table>
| 021323, 01/11/2019 | Escitalopram (1) | Psychiatry | CYP2D6 | Drug Interactions | 7 DRUG INTERACTIONS 7.19 Drugs Metabolized by Cytochrome P4502D6 In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. (…)

| 021323, 01/11/2019 | Escitalopram (2) | Psychiatry | CYP2C19 | Adverse Reactions | 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience ECG Changes (…) Based on the established exposure-response relationship, the predicted QTcF change from placebo arm (95% confidence interval) under the Cmax for the dose of 20 mg is 6.6 (7.9) msec. Escitalopram 30 mg given once daily resulted in mean Cmax of 1.7-fold higher than the mean Cmax for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.

| 022101, 06/07/2018 | Esomeprazole | Gastroenterology | CYP2C19 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS 7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

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<tr>
<td>206488, 10/11/2018</td>
<td>Eteplirsen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>(…) Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John’s Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John’s Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers (Cmax and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (Cmax and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John’s Wort or rifampin with NEXIUM.</td>
</tr>
<tr>
<td>022334, 04/10/2018</td>
<td>Everolimus (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: 1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2 negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.</td>
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</table>
| 022334, 04/10/2018                     | 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 | 1 INDICATIONS AND USAGE
1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer
AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

2 DOSAGE AND ADMINISTRATION
2.2 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer
The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.

5 WARNINGS AND PRECAUTIONS
5.8 Geriatric Patients
In the randomized hormone receptor-positive, HER2-negative breast cancer study (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)).

6 ADVERSE REACTIONS
6.1 Clinical Study Experience
Hormone Receptor-Positive, HER2 Negative Breast Cancer
The safety of AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily) (n = 488) vs. placebo in combination with exemestane (n = 238) 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:
1. Hormone receptor-positive, HER2-negative breast cancer (…)
2.5 Geriatric Use
In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness were observed between elderly and younger patients. (…)

12 CLINICAL PHARMACOLOGY
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. (…)
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<td>020753, 05/18/2018</td>
<td>Exemestane</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Adjuvant Treatment of Postmenopausal Women AROMASIN is indicated for adjuvant treatment of postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Clinical Studies (14.1).) (…) 2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dose The recommended dose of AROMASIN in early and advanced breast cancer is one 25 mg tablet once daily after a meal. • adjuvant treatment of postmenopausal women with estrogen receptor-positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy. (…) 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 = 0.65, 95% CI: 0.53, 0.79, P = 0.00001) in the AROMASIN arm compared to the tamoxifen arm. Consistent results were observed in the subgroups of patients with node negative or positive disease, and patients who had or had not received prior chemotherapy. (See Table 5) (…)</td>
</tr>
<tr>
<td>0202030, 11/21/2017</td>
<td>Fesoterodine</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.2 CYP3A4 Inhibitors Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clindamycin. Coadministration of the potent CYP3A4 inhibitor ketoconazole with fesoterodine led to approximately a doubling of the maximum concentration (Cmax) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of fesoterodine. Compared with CYP2D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole [see Clinical Pharmacology (12.3), Warnings and Precautions (5.8), and Dosage and Administration (2)]. (…) 7.4 CYP2D6 Inhibitors The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors. 12 CLINICAL PHARMACOLOGY 12.3 Pharmacodynamics Cardiac Electrophysiology (…) Electrocardiographic parameters were measured over a 24-hour period at pre-dose, after the first administration, and after the third administration of study medication. Fesoterodine 28 mg was chosen because this dose, when administered to CYP2D6 extensive metabolizers, results in an exposure to the active metabolite that is similar to the exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg together with CYP3A4 blockade. (…)</td>
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| 022526, 08/18/2015                      | Flibanserin (1) | Gynecology | CYP2C9 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.5 Pharmacogenomics  
Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes.  
CYP2C9 Poor Metabolizers  
A study comparing flibanserin exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C9 inhibitor. In 8 women who were poor metabolizers of CYP2C9, Cmax and AUC0-inf of flibanserin 100 mg once daily decreased 23% and 18%, compared to exposures among 8 extensive metabolizers of CYP2C9. |
| 022526, 08/18/2015                      | Flibanserin (2) | Gynecology | CYP2C19 | Adverse Reactions, Use in Specific Populations, Clinical Pharmacology | 6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Syncope in Poor CYP2C9 Metabolizers  
In a pharmacogenomic study of 100 mg ADDYI in subjects who were poor or extensive CYP2C9 metabolizers, syncope occurred in 1/9 (11%) subjects who were CYP2C9 poor metabolizers (this subject had a 3.2 fold higher flibanserin exposure compared to CYP2C9 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C9 extensive metabolizers [see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)].  
6.7 USE IN SPECIFIC POPULATIONS  
8.7 CYP2C9 Poor Metabolizers  
CYP2C9 poor metabolizers had increased flibanserin exposures compared to CYP2C9 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C9 poor metabolizer [see Adverse Reactions (6.1) and Clinical Pharmacology (12.5)]. Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C9 poor metabolizers. The frequencies of poor CYP2C9 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians. |
| 022526, 08/18/2015                      | Flibanserin (3) | Gynecology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.5 Pharmacogenomics  
Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes.  
CYP2C9 Poor Metabolizers  
A study comparing flibanserin exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C9 inhibitor. In 9 women who were poor metabolizers of CYP2C9, Cmax and AUC0-inf of flibanserin 100 mg once daily increased 1.5-fold (1.1-2.1) and 1.3-fold (0.9-2.1), compared to exposures among 8 extensive metabolizers of CYP2C9. Flibanserin half-life was increased from 11.1 hours in the extensive metabolizers of CYP2C9 to 13.5 hours in the poor metabolizers of CYP2C9 [see Adverse Reactions (6.1) and Use in Specific Populations (8.7)].  
The frequencies of poor metabolizers of CYP2C9 are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians. |
| 020985, 12/16/2003                      | Fluorouracil (1) | Dermatology | DPYD | Contraindications, Warnings | CONTRAINDICATIONS  
(….) Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catalyzed by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. (….)  
WARNINGS  
The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive. Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.  
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 topically applied fluorouracil.  
Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. |

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| 012209, 07/29/2016 | Fluorouracil (2) | Oncology | DPYD | Warnings and Precautions, Patient Counseling Information | 5 WARNINGS AND PRECAUTIONS
5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase (DPD) Activity

Based on post-marketing reports, patients with certain homogeneous 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.

17 PATIENT COUNSELING INFORMATION

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

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

Drug Interactions

Dysrhythmia Risk:

Drugs metabolized by CYP2D6: Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antihistamines (e.g., propafenone, flecainide, and others) should be approached with caution.

A decrease in plasma levels of the active enantiomer of CYP2D6 substrates has been observed in patients receiving fluoxetine (such as warfarin and phenytoin), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.

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.

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

12.3 Pharmacokinetics

Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.

| 018554, 07/23/2001 | Flutamide | Oncology | G6PD | Warnings | WARNINGS

Aniline Toxicity:

One metabolite of flutamide is 4-nitro-3-fluoromethylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (e.g., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methemoglobin levels should be considered.

| 020207, 05/29/2019 | Formoterol (1) | Pulmonary | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Metabolism

(…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

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

12.3 Pharmacokinetics

Metabolism

(…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

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<td>020450, 01/04/2017</td>
<td>Fosphenytoin</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 CÉRÉBÝX) treatment. The onset of symptoms is usually within 28 days, but can occur later. CÉRÉBÝX 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 CÉRÉBÝX as an alternative for carbamazepine patients positive for HLA B<em>1502. The use of HLA B</em>1502 genotyping has important limitations and may not 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>022033, 01/04/2017</td>
<td>Fluvoxamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS 7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes (…) Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as “poor metabolizers” (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an in vivo study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 “extensive metabolizers” (EM); mean Cmax, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patient known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine).</td>
</tr>
<tr>
<td>021344, 05/20/2019</td>
<td>Fulvestrant (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE Monotherapy FASLODEX is indicated for the treatment of: • HR-positive advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or • HR-positive postmenopausal women with disease progression following endocrine therapy. Combination Therapy FASLODEX is indicated for the treatment of: • HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy. • HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Combination Therapy with Palbociclib (PALOMA-3) The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months. (…) 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 510 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. The median duration of treatment was 15.8 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (…) 14 CLINICAL STUDIES Comparison of FASLODEX 500 mg and Anastrozole 1 mg (FALCON) A randomized, double-blind, double-dummy, multi-center study (FALCON, NCT01602380) of FASLODEX 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-positive, HER2-negative locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy. (…) Combination Therapy</td>
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<td>05/20/2019</td>
<td>Fulvestrant (2)</td>
<td>Oncology</td>
<td>ESR, PGR  (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>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) was an international, randomized, double-blind, parallel group, multi-center study of FASLODEX plus palbociclib versus FASLODEX plus placebo 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. (…) FASLODEX 500 mg in Combination with Albiglutide 150 mg (MONARCH 2) 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 albiglutide versus FASLODEX plus placebo. (…) Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy. FASLODEX 500 mg in Combination with Ribociclib 600 mg (MONALEESA-3) was a randomized double-blind, placebo-controlled study of FASLODEX plus ribociclib versus FASLODEX plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)</td>
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<td>021169, 02/14/2017</td>
<td>Galantamine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy. FASLODEX 500 mg in Combination with Palbociclib 125 mg (PALOMA-3) was a randomized, placebo-controlled, multi-center study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in patients with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…) FASLODEX 500 mg in Combination with Amanicabib 150 mg (MONARCH 2) was randomized, placebo-controlled, multi-center study conducted in patients 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. (…)</td>
</tr>
<tr>
<td>206955, 08/22/2018</td>
<td>Gefitinib (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage, Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE (1) IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [see Clinical Studies (14)]. Limitation of Use: Safety and efficacy of IRESSA 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</td>
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<td>206995, 08/22/2018</td>
<td>Gefitinib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>CYP2D6 Poor metabolizer: Gefitinib 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 to 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 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)).</td>
</tr>
<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 INICATIONS 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. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow (see Clinical Studies (14)). Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 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 I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. (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 3.6 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>
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<tr>
<td>020496, 12/21/2018</td>
<td>Glimepiride</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS 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 (5.2)). 6 ADVERSE REACTIONS 6.2 Postmarketing Experience The following adverse reactions have been identified during post-approval use of AMARYL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. (…) • Hemolytic anemia in patients with and without G6PD deficiency (see Warnings and Precautions (5.3)) (…)</td>
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<tr>
<td>017763, 08/18/2016</td>
<td>Glibizide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Hemolytic Anemia</td>
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<td>020051, 06/28/2017</td>
<td>Ibrutinib</td>
<td>Endocrinology</td>
<td>Nonspecific (NAT)</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 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>
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<td>019728, 02/12/2015</td>
<td>Goserelin</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</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>
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<td>020727, 03/12/2019</td>
<td>Hydralazine</td>
<td>Cardiology</td>
<td>Nonspecific</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY: 12.3 Pharmacokinetics: Absorption: (...) Hydralazine hydrochloride: About 2/3 of a 50-mg dose of 14C-hydralazine hydrochloride given in gelatin capsules was absorbed in hypertensive subjects. In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to 26%, with the higher percentages in slow acetylators. Administration of doses escalating from 75 mg to 1000 mg over three times daily to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-linear kinetics of hydralazine, probably reflecting saturable first pass metabolism. (...) Metabolism: Hydralazine is metabolized by acetylation, ring oxidation and conjugation with endogenous compounds including pyruvic acid. Acetylation occurs predominantly during the first-pass after oral administration which explains the dependence of the absolute bioavailability on the acetylator phenotype. About 50% of patients are fast acetylators and have lower exposure. (...)</td>
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<tr>
<td>009768, 01/27/2017</td>
<td>Hydroxychloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS: (...) PLAQUEVINIL should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…) ADVERSE REACTIONS: Blood and lymphatic system disorders: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolyis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…)</td>
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<td>205552, 01/25/2019</td>
<td>Ibrutinib (1)</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: 1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [see Clinical Studies (14.2)].</td>
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<td>Ibrutinib (2)</td>
<td>Oncology</td>
<td>Chromosome 11q</td>
<td>Clinical Studies</td>
<td>The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutilated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy include: lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%). (...) In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].</td>
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<tr>
<td>022192, 02/23/2017</td>
<td>Iloperidone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.2 Dosage in Special Populations Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6 FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 [see Clinical Pharmacology (12.3)].</td>
</tr>
<tr>
<td>021568, 08/21/2018</td>
<td>Imatinib (1)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Indications and Usage, Dosage and Administration</td>
<td>1 INDICATIONS AND USAGE 1.6 Aggressive Systemic Mastocytosis (ASM) Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test [see Dosage and Administration (2.7)] or with c-Kit mutational status unknown.</td>
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|                                        |      | Oncology         | BCR-ABL1 (Philadelphia chromosome) | Administration, Clinical Studies | 1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)  
Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.  
1.19 Adjuvant Treatment of GIST  
Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST. |
| 021588, 08/21/2018                     | Imitinib (2) |                             | | | |

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

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

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Fluid Retention and Edema
(…) In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Gleevec and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Gleevec and in 3.9% of patients receiving nilotinib 300 mg bid. (…) In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. In another randomized trial with newly diagnosed Ph+ CML patients in chronic phase that compared Gleevec and nilotinib, cardiac failure was observed in 1.1% of patient in the Gleevec arm and 2.2% of patients in the nilotinib 300 mg bid arm and severe (Grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. (…)

5.5 Hemorrhage
(…) Gastrintestinal 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 chronic phase comparing Gleevec versus IFN+ara-C, and in 12.5% of patients receiving Gleevec in the randomized trial of newly diagnosed patients with Ph+ CML in chronic phase comparing Gleevec versus IFN+ara-C, and in 12.5% of patients receiving 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. (See Table 3) (…)

6.2 Adverse Reactions in Pediatric Population
In combination with multi-agent chemotherapy:
(…) Patients with Ph+ ALL (n=92) were assigned to receive Gleevec and treated in 5 successive cohorts. Gleevec exposure was systematically increased in successive cohorts by earlier introduction and more prolonged duration.

6.3 Adverse Reactions in Pediatric Population
The safety of Gleevec given in combination with intensive chemotherapy was evaluated by comparing the incidence of grade 3 and 4 adverse events, neutropenia (less than 500/mcL), and thrombocytopenia (less than 75,000/mcL) in the 92 patients with Ph+ CML compared to 65 patients with Ph- ALL enrolled on the trial who did not receive Gleevec. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Gleevec. The protocol included up to 16 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Gleevec and 647 without Gleevec. The adverse events that were reported with a 5% or greater incidence in patients with Ph+ ALL compared to Ph- ALL or with a 1% or greater incidence in cycles of therapy that included Gleevec are presented in Table 8. (See Table 8) (…)

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

6.7 Hyperesinophilic Syndrome and Chronic Eosinophilic Leukemia
The safety profile of the HES/CEL patient population does not appear to be different from the safety profile of Gleevec observed in other hematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CT 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.

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<tr>
<td></td>
<td>021588, 08/21/2018</td>
<td>Imatinib (3)</td>
<td>Oncology</td>
<td>PDGFRB</td>
<td>1 INDICATIONS AND USAGE</td>
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<td></td>
<td>1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)</td>
<td>Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)].</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
<td>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 <a href="http://www.fda.gov/companiondiagnostics">http://www.fda.gov/companiondiagnostics</a>. The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.</td>
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<td>14 CLINICAL STUDIES</td>
<td>14.5 Myelodysplastic/Myeloproliferative Diseases An open-label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with ABL, Kit or PDGFR protein tyrosine kinases. (…) Sixteen patients had a translocation, involving chromosome 5q33 or 4q12, resulting in a PDGFR gene rearrangement. All of these patients responded hematologically (13 complete). Cyto genetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1 (7%) out of 14 patients experienced a hematologic response.</td>
</tr>
</tbody>
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</table>
| 021588, 08/21/2018                      | Imatinib (4) | Oncology | FIP1L1-PDGFRα | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)  
Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemias who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.  
2.7 Adult Patients with ASM  
Determine D816V c-Kit mutation status prior to initiating treatment. Information on FDA-approved test for the detection of D816V c-Kit mutation is available at http://www.fda.gov/comparisons/diagnostics. The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If cKit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 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 treated with FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.  
2.14 Dose Adjustment for Hematologic Adverse Reactions  
Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (…)  
14 CLINICAL STUDIES  
14.6 Aggressive Systemic Mastocytosis  
(…) Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this tyrosine kinase abnormality were predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a K2 mutation in the juxtamembrane region (one Phe522Cys and one K599I) and four patients had a D816V c-Kit mutation (not considered sensitive to Gleevec), one with concomitant CML. (See Table 23) (…)  
14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia  
One open-label, multicenter phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) (…) Ten patients had the PDGFR B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. (See Table 25) (…) (…) For the 10 patients with the PDGFB 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. |
| 017090, 07/28/2014                      | Imipramine | Psychiatry | CYP2D6 | Precautions | PRECAUTIONS  
Drug Interactions  
Drugs Metabolized by P450 2D6  
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). (…) |
| 022833, 05/29/2019                     | Indacaterol | Pulmonary | UGT1A1 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.4 Pharmacogenomics  
The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as `28) and in the (TA)6, (TA)6 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure. |

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<td>TTR</td>
<td>Adverse Reactions, Clinical Pharmacology</td>
<td>6 ADVERSE REACTIONS</td>
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<td></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 Val30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different other point mutations. (…)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics</td>
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<td>The pharmacodynamic effects of TEGSEDI were evaluated in HATTR amyloidosis patients treated with 284 mg TEGSEDI via subcutaneous injection once weekly.</td>
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<td>With repeat dosing, the mean percent decreases from baseline in serum TTR from Week 13 to Week 65 of treatment ranged from 68% to 74% (median range: 75% to 79%). Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race. (…)</td>
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<tr>
<td>761040, 08/17/2017</td>
<td>Inotuzumab Ozogamicin</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>Patients With Relapsed or Refractory ALL – INO-VATE ALL</td>
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<td>Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. All patients were required to have ≥ 5% bone marrow blasts and to have received 1 or 2 previous induction chemotherapy regimens for ALL. Patients with Philadelphia chromosome-negative B-cell precursor ALL were required to have disease that failed treatment with at least 1 tyrosine kinase inhibitor and standard chemotherapy. (…)</td>
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<td>(…) The median age was 47 years (range: 18-79 years), 276 patients (85%) had Philadelphia chromosome-negative ALL, 206 patients (63%) had a duration of first remission &gt; 12 months, and 55 patients (17%) had undergone a HSCT prior to receiving BESPONSA or Investigator’s choice of chemotherapy. (…)</td>
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<td>125377, 05/08/2019</td>
<td>Ipilimumab (1)</td>
<td>Oncology</td>
<td>HLA-A</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.1 Unsectetable or Metastatic Melanoma</td>
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<td>The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094653) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund’s adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. (…)</td>
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<tr>
<td>125377, 05/08/2019</td>
<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>
<td>1 INDICATIONS AND USAGE</td>
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<td>1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer</td>
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<td>YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (see Clinical Studies (14.4]). This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIA (&gt;1 mm nodal involvement), IIB, 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. (…)</td>
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<td>Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer</td>
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<td>The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, nonrandomized, multiple parallel-cohort study. In CHECKMATE-142, 119 patients with previously treated MSI-H or dMMR mCRC received YERVOY, in combination with nivolumab, in a single-arm cohort. In another single-arm cohort under CHECKMATE-142, 74 patients with mCRC received nivolumab monotherapy. (See Tables 9 and 10)(…)</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.4 Pediatric Use</td>
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<td>The safety and effectiveness of 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. (…)</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer</td>
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<td>CYB5R</td>
<td>Overdosage</td>
<td>OVERDOSAGE Methemoglobinemia</td>
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<td>05/07/2019</td>
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<td>Infectious Diseases</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Contraindications</td>
<td>CONTRAINDICATIONS Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.</td>
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<tr>
<td>020215, 10022014</td>
<td>Isosorbide Mononitrate</td>
<td>Cardiology</td>
<td>CYB5R</td>
<td>Overdosage</td>
<td>Methemoglobinemia</td>
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<td></td>
<td>Methemoglobinemia reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrates liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin to methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8-6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinism is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.</td>
</tr>
</tbody>
</table>

| 203188, 04/29/2019                      | Ivacaftor                    | Pulmonary        | CFTR       | Indications and Usage | KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. |

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<td>Placebo-controlled clinical trials established efficacy and safety in the following pediatric patients with CF:</td>
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<td>*(i) 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)]. *(ii) 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)]. <em>(…)</em></td>
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<td><strong>12 CLINICAL PHARMACOLOGY</strong></td>
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<td><strong>12.1 Mechanism of Action</strong></td>
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<td>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 electrophysioloogy 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 Table 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 in vitro CFTR chloride response threshold, are listed in Table 1 below the dotted line. (see Figure 1)</td>
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<td>Note that splice mutations cannot be studied in this FRT assay and are not included in Table 1. Evidence of clinical efficacy exists for non-canonical splice mutations 2789+5G→A, 3272–26A→G, 3849+10kbC→T, 711+3A→G and E831X and these are listed in Table 3 below [see also Clinical Studies (14.3)]. (see Table 6) (…)*</td>
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<td><strong>14 CLINICAL STUDIES</strong></td>
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<td><strong>14.1 Trials in Patients with CF who have a G551D Mutation in the CFTR Gene</strong></td>
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<td>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, parallel-group 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. <em>(…)</em></td>
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<td><strong>14.2 Trials in Patients with CF who have an R117H Mutation in the CFTR Gene</strong></td>
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<td>Efficacy and safety of KALYDECO in patients with CF who have an R117H mutation in the CFTR gene were evaluated in a randomized, double-blind, placebo-controlled, parallel-group clinical trial (Trial 5). (See Table 7) <em>(…)</em></td>
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<td><strong>14.3 Trials in Patients Homozygous for the F508del Mutation in the CFTR Gene</strong></td>
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<td>Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV1 ≤40% predicted. <em>(…)</em></td>
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<td>The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1. The treatment difference from placebo for the mean absolute change in percent predicted FEV1 through Week 16 in patients with CF homozygous for the</td>
</tr>
</tbody>
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<td>206333, 06/15/2018</td>
<td>Ivacaftor and Lumacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>F508del mutation in the CFTR gene was 1.72 percentage points (1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively) and did not reach statistical significance (Table 9). (See Table 9) (…)</td>
</tr>
<tr>
<td>210491, 02/12/2018</td>
<td>Ivacaftor and Tezacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. Limitations of Use The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation.</td>
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<tr>
<td><strong>022065, 10/18/2011</strong></td>
<td>Ixabepilone (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Clinical Studies</td>
<td>TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)].</td>
</tr>
<tr>
<td><strong>022065, 10/18/2011</strong></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 48% 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 43%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%. (…)</td>
</tr>
<tr>
<td><strong>204839, 04/28/2016</strong></td>
<td>Lacosamide</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Special Populations CYP2C19 Polymorphism There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. Results from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=6) of cytochrome P450 (CYP) 2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations and the amount excreted into urine of the O-desmethyl metabolite were about 70% reduced in PMs compared to EMs.</td>
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<tr>
<td>020406, 06/07/2018</td>
<td>Lansoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS  7.3 Tacrolimus  Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.</td>
</tr>
<tr>
<td>020209, 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:  • 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.  • letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.  TYKERB® in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer. 2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosing  HER2-Positive Metastatic Breast Cancer  The recommended dose of TYKERB® is 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. TYKERB® should be taken at least one hour before or one hour after a meal. The dose of TYKERB® should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)].  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>
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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>Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (…)</td>
</tr>
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</table>

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab. (…) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+), and 95% were ErbB2 IHC 3+ or 2+. (…) Clinical Studies Describing Limitation of Use: In two randomized trials, TYKERB based chemotherapy regimens have shown to be less effective than trastuzumab-based chemotherapy regimens. The first randomized, open-label study compared the safety and efficacy of TYKERB in combination with capecitabine relative to trastuzumab in combination with HER2-positive metastatic breast cancer (N = 549). (…) The second randomized, open-label study compared the safety and efficacy of taxane-based chemotherapy plus trastuzumab as first-line therapy in women with HER2-positive, metastatic breast cancer (N = 652). (…) Therapeutic 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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<tr>
<td><strong>6.1 Clinical Trials Experience</strong></td>
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<tr>
<td>(...) Hormone Receptor-Positive, Metastatic Breast Cancer: In a randomized clinical trial of patients (N = 1,286) with hormone receptor-positive, metastatic breast cancer, who had not received chemotherapy for their metastatic disease, patients received letrozole with or without TYKERB. (...)</td>
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<tr>
<td><strong>6.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer</strong></td>
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<tr>
<td>(...) 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-positive metastatic breast cancer (MBC) which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies patients received TYKERB with trastuzumab and an aromatase inhibitor (AI) (letrozole, exemestane, or anastrozole), TYKERB with an AI, or trastuzumab with an AI. (...)</td>
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<tr>
<td><strong>8 USE IN SPECIFIC POPULATIONS</strong></td>
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<td><strong>8.5 Geriatric Use</strong></td>
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<td>Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 5% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (...)</td>
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#### 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 ERbB2 IHC 3+ or IHC 2+ with FISH confirmation. (...)  

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

The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). (...)  

(...) In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (...)  

**14.3 HER2-negative 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-positive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior hormonal therapies and endocrine therapies. (...)  

#### 12 CLINICAL PHARMACOLOGY

**12.5 Pharmacogenomics**

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,184). Severe liver injury (ALT >5 times the upper limit of normal, NCI-CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DQA1*02:01 or DRB1*07:01 allele carriers was 8% versus 0.5% in non-carriers. These HLA alleles are present in approximately 15% to 25% of Caucasian, Asian, African, and Hispanic populations and 1% in Japanese populations. Liver function should be monitored in all patients receiving therapy with TYKERB regardless of genotype.  

#### 8 USE IN SPECIFIC POPULATIONS

**8.5 Geriatric Use**

Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 5% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (...)  

#### 14.3 HER2-negative 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-positive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior hormonal therapies and endocrine therapies. (...)  

#### 6 ADVERSE REACTIONS

**6.1 Clinical Trials Experience**

(...) Hormone Receptor-Positive, Metastatic Breast Cancer: In a randomized clinical trial of patients (N = 1,286) with hormone receptor-positive, metastatic breast cancer, who had not received chemotherapy for their metastatic disease, patients received letrozole with or without TYKERB. (...)  

**6.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer**

The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). (...)  

(...) In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (...)  

**6.3 HER2-negative 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-positive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior hormonal therapies and endocrine therapies. (...)  

### Footnotes

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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>Lenalidomide</td>
<td>Hematology</td>
<td>IFN3 (IL28B)</td>
<td>Clinical Studies</td>
<td>(…). The assessment of efficacy was based on the first 55 patients with solid tumors with an NTRK gene fusion enrolled across the three clinical trials. (…). The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infallile fibrosarcoma (13%), and thyroid cancer (9%). A total of 50 patients had NTRK gene fusions detected by NGS and 5 patients had NTRK gene fusions detected by FISH. Efficacy results are summarized in Tables 4, 5, and 6.</td>
</tr>
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</table>
| Ledipasvir and Sofosbuvir | Infectious Diseases | | | 14 CLINICAL STUDIES 14.2 Clinical Trials in Subjects with Genotype 1 HCV Treatment-Naive Adults without Cirrhosis — ION-3 (Study 0108) (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated subjects, the median age was 55 years (range: 20 to 75); 58% of the subjects were male; 78% were White; 6% were Black; 9% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 19 to 50 kg/m^2); 55% had baseline HIV RNA levels greater than or equal to 800,000 IU per mL; 68% had genotype 1a HIV infection; 73% had non-C/C IL28B alleles (CT or TT); (…) Treatment-Naive Adults with or without Cirrhosis — ION-2 (Study 0109) (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 65 treated subjects, the median age was 54 years (range: 18 to 87); 50% of the subjects were male; 80% were White; 12% were Black; 12% were Hispanic or Latino; mean body mass index was 27 kg/m^2 (range: 18 to 48 kg/m^2); 79% had baseline HIV RNA levels greater than or equal to 800,000 IU per mL; 67% had genotype 1a HIV infection; 70% had non-C/C IL28B alleles (CT or TT); and 16% had cirrhosis. (…) Previous-Treated Adults with or without Cirrhosis — SIRUS (Study 0121) (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomized subjects, the median age was 56 years (range: 23 to 77); 74% of the subjects were male; 97% were White; mean body mass index was 27 kg/m^2 (range: 19 to 47 kg/m^2); 63% had genotype 1a HIV 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. (…) 14.4 Clinical Trials in Subjects Co-infected with HIV and HCV-1 (…) Of the 335 treated subjects, the median age was 52 years (range: 26 to 72); 82% of the subjects were male; 61% were White; 34% were Black; mean body mass index was 27 kg/m^2 (range: 16 to 66 kg/m^2); 75% had genotype 1a HIV infection; 2% had genotype 4 infection; 76% 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 38% were non-responders. (See Table 14) (…) Previously-Treated Adults with Cirrhosis — SIRUS (Study 0121) (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomized subjects, the median age was 56 years (range: 23 to 77); 74% of the subjects were male; 97% were White; mean body mass index was 27 kg/m^2 (range: 19 to 47 kg/m^2); 63% had genotype 1a HIV 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. (…) BOXED WARNING WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM Hematologic Toxicity (Neutropenia and Thrombocytopenia) REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had a dose delay/reduction during the major study. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [see Dosage and Administration (2.2)]. 1 INDICATIONS AND USAGE 1.2 Myelodysplastic Syndromes REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Myelodysplastic Syndromes A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. Neutropenia (41.5%, 91/148) and neutropenia (58.8%, 87/148) were the most frequently reported adverse effects. The next most common adverse events observed were diarrhea (48.6%, 72/148), pruritus (41.9%, 62/148), rash (35.8%, 53/148) and fatigue (31.1%, 46/148). Table 8 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 9 summaries 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) * Therapeutic areas do not necessarily reflect the CDER review division. † Represented biomarkers are labeled 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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| 207988, 12/22/2015                     | Lesinurad | Rheumatology | CYP2C9 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS  
7.1 CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 Inducers  
Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiroidone), and in CYP2C9 poor metabolizers [see Clinical Pharmacology (12.3)] (…). |
| 020726, 04/05/2018                     | Letrozole | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Adjuvant Treatment of Early Breast Cancer  
Femara (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. |

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| 021451, 11/02/2018                     | Lidocaine and Prilocaine (1) | Anesthesiology    | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions                                 | 5 WARNINGS AND PRECAUTIONS 5 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 021451, 11/02/2018                     | Lidocaine and Prilocaine (2) | Anesthesiology    | G6PD                                 | Warnings and Precautions, Clinical Pharmacology          | 5 WARNINGS AND PRECAUTIONS 5 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 021623, 11/02/2018                     | Lidocaine and Tetracaine (1) | Anesthesiology    | G6PD                                 | Warnings and Precautions                                 | 5 WARNINGS AND PRECAUTIONS 5 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 021623, 11/02/2018                     | Lidocaine and Tetracaine (2) | Anesthesiology    | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions, Patient Counseling Information | 5 WARNINGS AND PRECAUTIONS 5 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 209229, 05/16/2018                     | Lofexidine                  | Anesthesiology    | CYP2D6                               | Use in Specific Populations                              | 8 USE IN SPECIFIC POPULATIONS 8.8 CYP2D6 Poor Metabolizers Although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–5% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) (see Clinical Pharmacology (12.3)).
| 210868, 11/02/2018                     | Lorlatinib (1)              | Oncology          | ALK                                 | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE LORBRENAR® 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. (…)
|                                        |                             |                   |                                      | 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience       |                |

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<td>ROS1</td>
<td>Adverse Reactions</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>(…) The data in Warnings and Precautions reflect exposure to LORBRENA in 332 patients with ALK-positive or ROS1-positive, metastatic non small cell lung cancer (NSCLC) enrolled in a multi-cohort, multinational, non-comparative, dose-finding, and activity-estimating trial (Study B7461001) who received LORBRENA at doses ranging from 10 mg to 200 mg daily in single or divided doses. The data described below reflect exposure to LORBRENA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA 100 mg orally once daily in Study B7461001. (…)</td>
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<td>F2 (Prothrombin)</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>SERPINC1 (Antithrombin III)</td>
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<td>Meclozine</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 meclozine exposure. Therefore, when ANTIVERT® is administered to patients with CYP2D6 polymorphism, monitor for adverse reactions and clinical effect accordingly.</td>
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<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>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>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 thiopeurine 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)]. 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 standard dosage) was as follows: homozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT<em>2, TPMT</em>3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. TPMT deficiency is detected in &lt;1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the TPMT gene, and approximately 21% have…</td>
</tr>
</tbody>
</table>

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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<td>205919, 02/20/2018</td>
<td>Mercaptopurine (2)</td>
<td>Oncology</td>
<td>NUDT15</td>
<td>Dosage and Administration, Warnings and Precautions, Clinical Pharmacology</td>
<td>one loss-of-function allele. The p.R139C variant of NUDT15 (present on the &quot;2&quot; and &quot;3&quot; alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient’s actual TPMT activity [see Dosage and Administration (2.2) and Warnings and Precautions (5.1)].</td>
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<tr>
<td>204630, 05/21/2018</td>
<td>Methylene Blue</td>
<td>Hematology</td>
<td>G6PD</td>
<td>Contraindications, Warnings and Precautions</td>
<td>4 CONTRAINDICATIONS PROVAYBLUE™ is contraindicated in the following conditions: • Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)]. • Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia [see Warnings and Precautions (5.3, 5.4)].</td>
</tr>
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<td>017854, 08/29/2017</td>
<td>Metoclopramide (1)</td>
<td>Gastroenterology</td>
<td>CYB5R</td>
<td>Use in Specific Populations</td>
<td>Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to aromatic amines such as aniline or sulfonamides 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, 2.3), Use in Specific Populations (8.9)).</td>
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<tr>
<td>017854, 08/29/2017</td>
<td>Metoclopramide (2)</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Use in Specific Populations, Overdosage</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.8 NADH-Cytochrome b5 Reductase Deficiency Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal (see Overdosage (10)).</td>
</tr>
<tr>
<td>017854, 08/29/2017</td>
<td>Metoclopramide (3)</td>
<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.2 Dosage for Gastroesophageal Reflux Reglan tablets may be administered continuously or intermittently in patients with symptomatic gastroesophageal reflux who fail to respond to conventional therapy: Continuous Dosing The recommended adult dosage of Reglan is 10 to 15 mg four times daily for 4 to 12 weeks. The treatment duration is determined by endoscopic response. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 60 mg. Table 1 displays the recommended 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 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)). 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Elimination Metabolism: Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monodeethylmetoclopramide, a major oxidative metabolite, is formed primarily by CYP2D6, an enzyme subject to genetic variability (see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.9)).</td>
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<td>019662, 05/06/2014</td>
<td>Metoprolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.2 CYP2D6 Inhibitors: Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.</td>
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</table>

| 207997, 06/21/2018                      | Midostaurin (1) | Oncology | FLT3 | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE 1.1 Acute Myeloid Leukemia: RYDAPT is indicated, in combination with standard cytoreductive and consolidation chemotherapy, for the treatment of adult patients with newly diagnosed FLT3-mutated AML who are FLT3 mutation-positive, as detected by a FDA approved test [see Dosage and Administration (2.1), Clinical Studies (14.1)]. (…) 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection: Select patients for the treatment of AML with RYDAPT based on the presence of FLT3 mutation positivity [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of FLT3 mutation in AML is available at: http://www.fda.gov/CompanionDiagnóstics.  |

| 207997, 06/21/2018                      | Midostaurin (2) | Oncology | NPM1 | Clinical Studies | 14 CLINICAL STUDIES 14.1 Acute Myeloid Leukemia: Study 1: RYDAPT in combination with chemotherapy was investigated in a randomized, double-blind placebo-controlled trial of 717 patients with newly-diagnosed FLT3-mutated AML. In this study, FLT3 mutation status was determined prospectively with a clinical trial assay and verified retrospectively using the companion diagnostic LeukoSleuth® CDx FLT3 Mutation Assay, which is an FDA-approved test for selection of patients with AML for RYDAPT treatment. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio less than 0.7, and ITD with allelic ratio greater than or equal to 0.7. (…) 14.2 Systemic Mastocytosis: Study 2: Of the 563 patients with NPM1 testing, 58% had an NPM1 mutation. The two treatment groups were generally balanced with respect to the baseline demographics and disease characteristics, except that the placebo arm had a higher percentage of females (59%) than in the midostaurin arm (52%). NPM1 mutations were identified in 55% of patients tested on the midostaurin arm and 60% of patients tested on the placebo arm. (…)  |

| 207997, 06/21/2018                      | Midostaurin (3) | Oncology | KIT | Clinical Studies | 14 CLINICAL STUDIES 14.2 Systemic Mastocytosis: Study 2: Of the 116 patients treated, a study steering committee identified 89 patients who had measurable C-findings and were evaluable for response. The median age in this group was 64 years (range: 25 to 82), 64% of patients were male, and nearly all patients (97%) were Caucasian. Among these patients, 36% had prior therapy for SM, and 82% had the KIT D816V mutation detected at baseline. Their median duration of treatment was 11 months (range: < 1 to 68 months), with treatment ongoing in 17% Efficacy was established on the basis of confirmed complete remission (CR) plus incomplete remission (ICR) by 6 cycles of RYDAPT by modified Valient criteria for ASMA and SM-HIV (Table 7). Table 7 shows responses to RYDAPT according to modified Valient criteria. Confirmed major or partial responses occurred in  |

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<td>Migalastat</td>
<td>Inborn Errors of Metabolism</td>
<td>GLA</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>46 of 73 patients with a documented KIT D816V mutation, 7 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. (…)</td>
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<td>07/26/2018</td>
<td>Mirabegron</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>1 INDICATIONS AND USAGE GALAFOLD™ is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data [see Clinical Pharmacology (12.1)]. (…)</td>
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<td>020098, 04/27/2018</td>
<td>Mivacurium</td>
<td>Anesthesiology</td>
<td>BCHE</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION • Select adults with confirmed Fabry disease who have an amenable GLA variant for treatment with GALAFOLD [see Table 2 in Clinical Pharmacology (12.1)]. • Treatment is indicated for patients with an amenable GLA variant that is interpreted by a clinical genetics professional as causing Fabry disease (pathogenic, likely pathogenic) in the clinical context of the patient. 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). (…)</td>
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<td>Cardiology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
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The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.1 to 0.2 mg/kg MIVACRON, the clinically effective duration of action was 8 minutes to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients. As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (one in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED10-20 in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

Administration of MIVACRON over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see PRECAUTIONS - Reduced Plasma Cholinesterase Activity and CLINICAL PHARMACOLOGY - Individualization of Dosages subsection).

**Individualization of Dosages**

**Reduced Plasma Cholinesterase Activity**

The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus, initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of MIVACRON are not recommended in homozygous patients. MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After an initial dose of 0.15 mg/kg MIVACRON, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotypes 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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<td>Nefazodone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity. Plasma levels of d-nebivolol increase in proportion to dose in EMs and PMs for doses up to 20 mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as d-nebivolol's β receptor affinity is &gt; 1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher Cmax and 10-fold higher AUC of d-nebivolol than do EMs. d-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.</td>
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<td>208051, 06/29/2018</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 NERLYNX is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy [see Clinical Studies (14)].</td>
</tr>
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| 208051, 06/26/2018 | Neratinib (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES 14.1 Extended Adjuvant Treatment in Breast Cancer The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. (…)

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience ExteNET The data described below reflect exposure of NERLYNX as a single agent in ExteNET, 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. (…)

14 CLINICAL STUDIES 14.1 Extended Adjuvant Treatment in Breast Cancer The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). (…)

022068, 08/21/2018 | Nilotinib (1) | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in | 1 INDICATIONS AND USAGE 1.1 Adult and Pediatric Patients with Newly Diagnosed Ph+ CML-CP Tasigna (nilotinib) is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. |

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<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<td>Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>Tasigna is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy.</td>
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</tr>
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</table>

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

The recommended dose of Tasigna is 300 mg orally twice daily.

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

The recommended dose of Tasigna is 400 mg orally twice daily.

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

The recommended dose of Tasigna for pediatric patients is 230 mg/m2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

2.2 Discontinuation of treatment after a sustained molecular response (MR4.5) on Tasigna

Patient Selection

Eligibility for Discontinuation of Treatment

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

Patients with typical BCR-ABL transcripts (i.e., 13a2/b2a2 or e14a2/b3a2) who achieve the sustained MR4.5 criteria are eligible for discontinuation of Tasigna treatment. Patients must continue to be monitored for possible loss of molecular remission after treatment discontinuation. Use the same FDA authorized test to consistently monitor molecular response levels while on and off treatment.

Consider discontinuation of treatment in patients with newly diagnosed Ph+ CML-CP who have:

- been treated with Tasigna for at least 3 years
- maintained a molecular response of at least MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01% IS) for one year prior to discontinuation of therapy
- achieved an MR4.5 for the last assessment taken immediately prior to discontinuation of therapy
- been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2)
- no history of accelerated phase or blast crisis
- no history of prior attempts of treatment-free remission discontinuation that resulted in relapse

Consider discontinuation of treatment in patients with Ph+ CML-CP that are resistant or intolerant to treatment with imatinib who have achieved a sustained molecular response (MR4.5) on Tasigna who have:

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

Monitor BCR-ABL transcript levels and complete blood count with differential in patients who have discontinued Tasigna therapy monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter [see Warnings and Precautions (5.16)]. Upon the loss of MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01%IS) during the treatment-free phase, monitor BCR-ABL transcript levels every 2 weeks until BCR-ABL levels remain lower than major molecular response (MMR, corresponding to MR3.0 or = BCR-ABL/ABL ≤ 0.1%IS) for 4 consecutive measurements.

The patient can then proceed to the original monitoring schedule.

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

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

2.4 Dosage Modification for QT Interval Prolongation

See Table 2 for dose adjustments for QT interval prolongation [see Clinical Pharmacology (12.2)]. (See Table 2) (…) 2.7 Dosage Modification for Hepatic Impairment

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

2.8 Dosage Modification with Concomitant Strong CYP3A4 Inhibitors

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<td>Avoid the concomitant use of strong CYP3A4 inhibitors. Should treatment with any of these agents be required, interrupt therapy with Tasigna. If patients must be coadministered a strong CYP3A4 inhibitor, reduce dosage to 300 mg once daily in patients with resistant or intolerant Ph+ CML-CP or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP. (…)</td>
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</tbody>
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### 5 WARNINGS AND PRECAUTIONS

#### 5.12 Hemorrhage

In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Tasigna and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Tasigna 300 mg bid arm and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Tasigna 300 mg bid and 400 mg bid arms and in 1.4% of patients in the imatinib arm, respectively. Grade 3 or 4 events occurred in 0.7% and 1.4% of patients in the Tasigna 300 mg bid and 400 mg bid arms, respectively, and in no patients in the imatinib arm.

#### 5.17 Fluid Retention

In the randomized trial in patients with newly diagnosed Ph+ CML in chronic phase, severe (Grade 3 or 4) fluid retention occurred in 3.9% and 2.9% of patients receiving Tasigna 300 mg bid and 400 mg bid, respectively, and in 2.5% of patients receiving imatinib. (…) 

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

**In Adult Patients with Newly Diagnosed Ph+ CML-CP**

The data below reflect exposure to Tasigna from a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the Tasigna 300 mg twice daily group was 61 months (range 0.1 to 71 months). The median actual dose intensity was 593 mg/day in the Tasigna 300 mg twice daily group. (…) (…)

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

In the single open-label multicenter clinical trial, a total of 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP=321; CML-AP=137) at the recommended dose of 400 mg twice daily. (…) (…)

**Most Frequently Reported Adverse Reactions**

Tables 7 and 8 show the percentage of adult patients experiencing non-hematologic adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in greater than 10% of adult patients who received at least 1 dose of Tasigna are listed. (See Tables 7 and 8) (…) (…)

**Laboratory Abnormalities**

Table 9 shows the percentage of adult patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna. (See Table 9) (…) (…)

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

The rate of musculoskeletal symptoms decreased in patients who entered the Tasigna treatment remission (NTRI) phase, at 11/88 (12.5%) in the newly diagnosed population and 14/56 (25%) in the population previously treated with imatinib. Other adverse reactions observed in the Tasigna treatment phase were similar to those observed Tasigna use in patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP. (See Table 10) (…) (…)

**Additional Data from Clinical Trials**

The following adverse drug reactions were reported in adult patients in the Tasigna clinical studies at the recommended doses. These adverse drug reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (greater than or equal to 1% and less than 10%), uncommon (greater than or equal to 0.1% and less than 1%), and unknown frequency (single events). For laboratory abnormalities, very common events (greater than or equal to 10%), which were not included in Tables 7 and 8, are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category, obtained from 2 clinical studies:

1. Adult patients with newly diagnosed Ph+ CML-CP 60 month analysis and.
2. Adult patients with resistant or intolerant Ph+ CML-CP and CML-AP 24 months’ analysis, (…) (…)

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

The data below reflect exposure to Tasigna from two studies in pediatric patients from 2 to less than 18 years of age with either newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP treated at the recommended dose of 230 mg/m² twice daily (n=69) [see Clinical Studies (14.5)]. The median time on treatment with Tasigna was 13.8 months (range: 0.7 to 30.9 months). The median actual dose intensity was 435.5 mg/m²/day (range: 149 to 517 mg/m²/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58%) had relative dose intensity superior to 90%.

**In pediatric patients with Ph+ CML-CP, the most common (greater than 20%) non-hematologic adverse drug reactions were headache, rash, hyperbilirubinemia, alanine aminotransferase increased, pyrexia, nausea, upper respiratory tract infection, aspartate aminotransferase increased, and vomiting. The most common (greater than 5%) Grade 3/4 non-hematologic adverse drug reactions were alanine aminotransferase increased and hyperbilirubinemia. (…)**

### 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 trials [see Clinical Studies (14.5)]. The 25 patients with newly diagnosed Ph+ CML-CP were in the following age groups: 6 children (age 2 to less than 12 years) and 19 adolescents (age 12 to less than 18 years).

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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 AUC(0-12h) were 2260 ng/ml (35%) and 18000 ng∙h/ml (33%), respectively. In adult patients with newly diagnosed Ph+ CML given Tasigna 300 mg twice daily, the steady-state mean (%CV) Cmax and AUC(0-12h) were 1540 ng/ml (48%) and 13337 ng∙h/ml (46%), respectively. (…)

12.3 Pharmacokinetics

Specific Populations

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

Pediatric Patients

Following administration of the approved recommend pediatric dosage of nilotinib, steady-state exposure of nilotinib were within 2-fold to adult patients treated with 400 mg twice daily. Steady-state Cmin was comparable across all age groups (pediatric patients from ages 2 to less than 18 years), diseases (patients with newly diagnosed and resistant or intolerant Ph+ CML) and studies.

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

14 CLINICAL STUDIES

14.1 Adult Newly Diagnosed Ph+ CML-CP

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

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

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

Study CAMN107A2101 (referred to as Study A2101) (NCT00109707) 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 median ages of the patients were 54 years for CML-CP and 49 years for CML-AP. Efficacy endpoints are summarized in Table 12. (…)

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

The ENESTfreedom (Evaluating Nilotinib Efficacy and Safety in clinical Trials-freedom) study (NCT01784068) is an open-label, multicenter, single-arm study, where 215 adult patients with Ph+ CML-CP treated with Tasigna in first-line for ≥ 2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 190 patients (88.4%) entered the “Treatment-free Remission” (TFR) phase after achieving a sustained major molecular response (MR4.5) during the consolidation phase, defined by the following criteria:

- The last quarterly assessment (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 65 years of age, 24.9% 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.

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

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<td>Nitrofurantoin</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>WARNINGS: 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-phosphatedehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn. ADVERSE REACTIONS&lt;br&gt;<strong>Laboratory Adverse Events</strong>&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><strong>208447, 03/27/2017</strong></td>
<td>Niraparib</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES&lt;br&gt;(…) Eligible patients were assigned to one of two cohorts based on the results of the BRCAAnalysis CDx. Patients with deleterious or suspected deleterious germline BRCA mutations (gBRCA) were assigned to the germline BRCA mutated (gBRCAmut) cohort (n=203), and those without germline BRCA mutations were assigned to the non-gBRCA mut cohort (n=350). (…) The trial demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the gBRCA mut cohort and the non-gBRCA mut cohort (See Table 6, Figures 1 and 2).</td>
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<td>BRAF</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
<td>Unresectable or Metastatic Melanoma</td>
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<td>6.1.1 Previous Treated Metastatic Melanoma</td>
<td>(… in CHECKMATE-037, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (…)</td>
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<td>6.1.2 Previously Untreated Metastatic Melanoma</td>
<td>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. (…)</td>
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<td>CD274 (PD-L1)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.2 Pharmacodynamics Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.</td>
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<tr>
<td><strong>14.2 Adjuvant Treatment of Melanoma</strong></td>
<td>CHECKMATE-238</td>
<td>(…) Randomization was stratified by PD-L1 status (positive [based on 5% level] vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage IIIb/IV vs Stage IV M1a-M1b vs Stage IV M1c). (…)</td>
<td>(…) 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%). (…)</td>
<td>(…)</td>
<td>(…)</td>
</tr>
<tr>
<td><strong>14.3 Metastatic Non-Small Cell Lung Cancer (NSCLC)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Second-line Treatment of Metastatic Squamous NSCLC</td>
<td>CHECKMATE-017</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Second-line Treatment of Metastatic Non-Squamous NSCLC</td>
<td>CHECKMATE-057</td>
</tr>
<tr>
<td><strong>14.4 Small Cell Lung Cancer</strong></td>
<td>CHECKMATE-032 (NCT01528394) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic solid tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinum-based chemotherapy to receive treatment with OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. (…)</td>
<td></td>
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<td>(…)</td>
<td></td>
</tr>
<tr>
<td><strong>14.5 Advanced Renal Cell Carcinoma</strong></td>
<td>CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior antiangiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. (…) OS benefit was observed regardless of PD-L1 expression level. (See Table 29) (…)</td>
<td></td>
<td></td>
<td>Previously Treated Renal Cell Carcinoma</td>
<td>CHECKMATE-214 (NCT02317456) was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. (…) OS benefit was observed regardless of PD-L1 expression level. (See Table 29) (…)</td>
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<td>Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with chl after failure of autologous HSCT. CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort study in chl. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation study that included chl. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. (…) Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with chl after failure of autologous HSCT. CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in chl. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included chl. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance &lt;40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity. (…)</td>
<td></td>
</tr>
<tr>
<td><strong>14.6 Classical Hodgkin Lymphoma</strong></td>
<td>CHECKMATE-025 (NCT01668784) 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. (…)</td>
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<td>Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance &lt;40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. (…)</td>
<td></td>
</tr>
<tr>
<td><strong>14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck</strong></td>
<td>CHECKMATE-141</td>
<td>Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the study population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as &lt;1% of tumor cells expressing PD-L1, and 57% (148/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified analyses were conducted in subgroups defined by PD-L1 expression. (…)</td>
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<td>(…)</td>
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<td>125554, 05/02/2019</td>
<td>Nivolumab</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>exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCC H subgroup. 14.8 Urothelial Carcinoma CHECKMATE-275 (…) Patients were included regardless of their PD-L1 status. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for prespecified analyses. Of the 270 patients, 48% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 52% of patients, were classified as having PD-L1 expression of &lt;1% (defined as &lt;1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 27. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%). (see Table 35)</td>
</tr>
<tr>
<td>018013, 04/09/2019</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 10% of Caucasians are so called &quot;poor metabolizers&quot;). Reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (…)</td>
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| 209531, 10/10/2018                     | Nusinersen | Neurology        | SMN2       | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants. |
| 125486, 11/16/2017                     | Obinutuzumab | Oncology | MS4A1 (CD20 antigen) | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Infantile-Onset SMA  
(…) Baseline demographics were balanced between the SPINRAZA and control groups with the exception of age at first treatment (median age 175 vs. 206 days, respectively). The SPINRAZA and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number.  
(…)  
14.3 Presymptomatic SMA  
(…) Some patients receiving SPINRAZA before the onset of SMA symptoms survived without requiring permanent ventilation while what would be expected based on their SMN2 copy number, and some patients also achieved age-appropriate growth and developmental milestones such as the ability to sit unassisted, stand, or walk. |
| 208558, 12/19/2018                     | Olaparib (1) | Oncology | BRCA       | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer  
Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  
1.3 Advanced gBRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy  
Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious 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)].  
1.4 Germline 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)]. |

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<td>Overall, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) in patients treated with Lynparza monotheapy in clinical trials, including long-term follow up, was &lt;1.5% (20/2258) and the majority of events had a fatal outcome. Of these, 22/26 patients had a documented BRCA mutation, 2 patients had gBRCA wildtype and in 2 patients the BRCA mutation status was unknown. (...)</td>
</tr>
</tbody>
</table>

**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 391 patients received either Lynparza 300 mg BID (n=260) or placebo tablets (n=131) 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. (…)

**Treatment of Advanced gBRCAm Ovarian Cancer After 3 or More Lines of Chemotherapy**

**Pooled data**

Treatment with Lynparza (capsule formulation) as monotherapy was studied in 223 patients (pooled from 6 studies) with gBRCAm advanced ovarian cancer who had received 3 or more prior lines of chemotherapy. (…)

**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**

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

**SOLO-1** (NCT01844886) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza with placebo in patients with BRCA-mutated (BRCAm) advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy in which 391 patients were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily (n=260) or placebo (n=131). (…)

**SOLO-2** (NCT01874353) was a double-blind, placebo-controlled trial in which patients (n=295) with gBRCAm ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy in which 391 patients were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily (n=260) or placebo (n=130). (…)

**14.2 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** (NCT01874353) was a double-blind, placebo-controlled trial in which patients (n=265) with gBRCAm ovarian, fallopian tube, or primary peritoneal cancer were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. (…)

**14.3 Advanced gBRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy**

The efficacy of Lynparza was also investigated in a single-arm study of patients with deleterious or suspected deleterious gBRCAm advanced cancers. A total of 137 patients with measurable, advanced gBRCAm ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules at a dose of 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST, version 1.0. (…)

**14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer**

**OlympiAD**

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| 208588, 12/19/2018                     | Olaparib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | **1 INDICATIONS AND USAGE**
1.4 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
Olaparib is indicated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjunct, 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)]. |

| 208588, 12/19/2018                     | Olaparib (3) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Clinical Studies | **1 INDICATIONS AND USAGE**
1.4 Germline 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, adjunct, 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)]. |

| 761038, 10/19/2016                     | Olaratumab | Oncology | PDGFRα | Clinical Studies | **14 CLINICAL STUDIES**
14.4 Treatment of gBRCA-mutation
Olaratumab is indicated in patients with deleterious or suspected deleterious gBRCA-mutation [see Indications and Usage (1.4) and Clinical Studies (14.3)]. |

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OlymipAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2-negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider’s choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. (…) No prior treatment with a PARP inhibitor was permitted. Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx™, and 297 confirmed to have deleterious or suspected deleterious gBRCAm status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider’s choice of chemotherapy arm. (…)

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. (…)

The proportions were balanced across treatment arms. (…)

Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors and the proportions were balanced across treatment arms. (…)

Endocrine therapy. (…) 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)].

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, adjunct, 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 INDICATIONS AND USAGE**

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

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**

**2.2 Recommended Dosing**

**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**

**14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer**

OlymipAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2-negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider’s choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. (…)

**14 CLINICAL STUDIES**

**14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer**

OlymipAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2-negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider’s choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. (…) Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].

**14 CLINICAL STUDIES**

**14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer**

OlymipAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2-negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider’s choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be 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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| 03/08/2017   | 90007           | Omeprazole    | CYP2C19   | Drug, Clinical Pharmacology | The efficacy of LARTRUVO 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 PDGFRα expression by an investigational use assay. Patients were randomized (1:1) to receive LARTRUVO in combination with doxorubicin or doxorubicin as a single agent. PDGFRα expression (positive versus negative); number of previous lines of treatment (0 versus 1 or more), histological tumor type (leiomyosarcoma versus synovial sarcoma versus all others), and ECOG PS (0 or 1 versus 2) were used to allocate patients in the randomization. (…)
| 02/0007,     | 03/08/2017      | Ondansetron   | CYP2D6    | Clinical Pharmacology      | The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolizers of CYP2D6 and those who were extensive metabolizers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo. (…)
| 02/0206,     | 08/21/2018      | Omeprazole    | CYP2C19   | Drug, Clinical Pharmacology | The efficacy of SYNRIBO was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+]) (whether lost or never achieved); or no major cytogenetic response (MCyR) by 52 weeks (i.e., ≥35% Ph+)(whether lost or never achieved); or progressive leukocytosis. (See Table 5)
| 14/2 CLINICAL STUDIES | 07/23/2018      | Ombitasvir, Paritaprevir, and Ritonavir | IFNL3 (IL28B) | Clinical Studies | The efficacy of SYNRIBO was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+]) (whether lost or never achieved); or no major cytogenetic response (MCyR) by 52 weeks (i.e., ≥35% Ph+)(whether lost or never achieved); or progressive leukocytosis. (See Table 5)
| 20/0007      | 03/08/2017      | Ondansetron   | CYP2D6    | Clinical Pharmacology      | The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolizers of CYP2D6 and those who were extensive metabolizers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo. (…)
| 20/0007      | 03/08/2017      | Ondansetron   | CYP2D6    | Clinical Pharmacology      | The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolizers of CYP2D6 and those who were extensive metabolizers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo. (…)

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<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
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#### 1 INDICATIONS AND USAGE

**1.1 First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)**

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)].

**1.2 Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC**

TAGRISSO is indicated for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1)].

#### 2 DOSAGE AND ADMINISTRATION

**2.1 Patient Selection**

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens [see Clinical Studies (14)]. Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TAGRISSO following progression on or after EGFR TKI therapy based on the presence of an EGFR T790M mutation in tumor or plasma specimens [see Clinical Studies (14)].

#### 6 ADVERSE REACTIONS

**6.1 Clinical Trials Experience**

(…)

The data described below reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) [see Warnings and Precautions (5)].

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

**6.2 Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer**

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. (…)

**6.3 Previously Treated EGFR T790M Mutation-Positive Metastatic Non-Small Cell Lung Cancer**

The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGFR T790M mutationpositive NSCLC who had progressive disease following first line EGFR TKI treatment. (…)

**6.4 AURA3 Trial**

**14 CLINICAL STUDIES**

**14.1 Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer**

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter, double-blind, active controlled trial (FLAURA [NCT02296125]) in patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, metastatic NSCLC, who had not received previous systemic treatment for metastatic disease. Patients were required to have measurable disease per RECIST v1.1, a WHO performance status of 0-1, and EGFR exon 19 deletion or exon 21 L858R mutation in tumor prospectively identified by the cobas® EGFR Mutation Test in a central laboratory or by an investigational assay at a CLIA-certified or accredited laboratory. (…)

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter double-blind, active controlled trial (FLAURA [NCT02296125]) in patients with EGFR exon 19 deletion or exon 21 L858R mutation type (exon 19 deletion or exon 21 L858R mutation) and ethnicity (Asian or non-Asian). Patients randomized to the control arm were offered TAGRISSO at the time of disease progression if tumor samples tested positive for the EGFR T790M mutation. (…)

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter open-label, active-controlled trial in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI (AURA3). All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas® EGFR Mutation Test performed in a central laboratory prior to randomization. (…)

**14.2 Previously Treated EGFR T790M Mutation-Positive Metastatic Non-Small Cell Lung Cancer**

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter open-label, active-controlled trial in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI (AURA3). All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas® EGFR Mutation Test performed in a central laboratory prior to randomization. (…)

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<tr>
<td>20305, 01/25/2019</td>
<td>Ospemifene (1)</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 Warfarin Ospemifene 60 mg was given after a light breakfast (two slices of bread with ham and cheese and juice) once daily for 12 days in sixteen postmenopausal women who were determined to be rapid metabolizers of CYP2C9 (CYP2C9*1/<em>1 or CYP2C9</em>1/*2). On Day 8, a single dose of warfarin 10 mg and vitamin K 10 mg was administered one hour after a light breakfast. The geometric mean ratio (90% CI) for S-warfarin with and without ospemifene for Cmax and AU0-inf were 0.97 (0.92-1.02) and 0.96 (0.91-1.00), respectively. Multiple doses of ospemifene did not significantly affect the pharmacokinetics of a single dose of warfarin. No study was conducted with multiple doses of warfarin.</td>
</tr>
<tr>
<td>20305, 01/25/2019</td>
<td>Ospemifene (2)</td>
<td>Gynecology</td>
<td>CYP2B6</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 Bupropion Ospemifene 60 mg was administered once daily for seven consecutive days after the evening meal in sixteen postmenopausal women (not homozygous for CYP2B6*6). On the Day 8 after overnight fast, a single 150 mg dose of sustained release bupropion was administered in morning under fasted condition. The geometric mean ratio (90% CI) for bupropion with and without ospemifene for Cmax and AU0-inf were 0.82 (0.75-0.91) and 0.81 (0.77-0.86), respectively. The geometric mean ratio (90% CI) for hydroxybupropion, an active metabolite formed via CYP2B6, with and without ospemifene for Cmax and AU0-inf were 1.16 (1.08-1.24) and 0.98 (0.92-1.04), respectively.</td>
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<tr>
<td>208110, 12/13/2018</td>
<td>Oxcarbazepine</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 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 HLA-B</em>1502 allele ranges from 2% to 12% in Han Chinese populations, is about 8% in Thai populations, and above 15% in the Philippines and in some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B<em>1502 allele is negligible in people from European descent, several African populations, 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 medical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been well characterized.</td>
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</table>
| 208032, 11/02/2018  | Oxymetazoline and Tetracaine (1) | Anesthesiology | G6PD | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
| 208032, 11/02/2018  | Oxymetazoline and Tetracaine (2) | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. |
| 207103, 04/04/2019  | Palbociclib (1) | Oncology | ESR (Hormone Receptor) | Indications and Usage. Adverse | 1 INDICATIONS AND USAGE |

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| 207103, 04/04/2019                     | Palbociclib (2) | Oncology | ERBB2 (HER2) | 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 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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| 021998, 01/25/2019                     | Paliperidone | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  
Metabolism and Elimination  
(…) Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. (…) |
| 021372, 09/18/2014                     | Palonosetron | Gastroenterology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  
Metabolism  
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-Hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates. |
| 125147, 06/29/2017                     | Panitumumab (1) | Oncology | EGFR | Adverse Reactions, Clinical Pharmacology, Clinical Studies | 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience  
(…) Safety data are presented from two clinical trials in which patients received Vectibix: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFIRI chemotherapy versus FOLFIRI 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. |
| 125147, 06/29/2017                     | Panitumumab (2) | Oncology | RAS | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE 1.1 Metastatic Colorectal Cancer  
Vectibix is indicated for the treatment of patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA- approved test for this use) metastatic colorectal cancer (mCRC) [see Dosage and Administration (2.1)]:  
• As first-line therapy in combination with FOLFIRI [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), 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.

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**

- Vectibix in Combination with FOLFOX Chemotherapy

The most commonly reported adverse reactions (≥ 20%) in patients with wild-type KRAS mCRC receiving Vectibix (6 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, acniform 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 was undetectable in 429 patients (93%) 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 receiving Vectibix (6 mg/kg every 2 weeks) and FOLFOX versus FOLFOX alone was 0.45 (95% CI: 0.34-0.59) favoring the panitumumab arm. The response rate was 17% for the panitumumab arm and 0% for BSC. There were no differences in OS; 77% of patients in the BSC arm received panitumumab at the time of disease progression.

Study 20080763 (NCT01001377)

Study 20080763 (NCT0131277) vs 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 BSC and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. The major efficacy outcome measure was OS in patients with wild-type KRAS mCRC. Secondary efficacy outcome measures included OS in the subgroup of patients with wild-type RAS mCRC; PFS and ORR in patients with wild-type KRAS; and PFS and ORR in the subgroup of patients with wild-type RAS mCRC.

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† Referenced 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 “Non-specific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.

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<td>(…) KRAS tumor mutation status was available for all patients and RAS tumor mutation status was available for 86% of the 377 patients. Among the 377 patients, 270 (72%) patients had wild-type RAS tumors, 54 (14%) had mutant RAS tumors, and 54 (14%) had unknown RAS tumor status. (See Table 4 and Figure 2). 14.2 First-line in Combination with FOLFAX Chemotherapy (…) The prespecified major efficacy measure was PFS in patients ( n = 656 ) with wild-type KRAS mCRC as assessed by a blinded independent central review of imaging. Other key efficacy measures included OS and ORR. In Study 20050203, in the wild-type KRAS subgroup ( n = 656 ), 64% of patients were men, 92% White, 2% Black, and 4% Hispanic or Latino. Sixty-six percent of patients had colon cancer and 34% had rectal cancer. ECOG performance was 0 in 56% of patients, 1 in 38% of patients, and 2 in 6% of patients. Median age was 61.5 years. The efficacy results in Study 20050203 in patients with wild-type KRAS mCRC are presented in Table 5 below. (See Table 5) (…) Exploratory Analysis of OS An exploratory analysis of OS with updated information based on events in 82% of patients with wild-type KRAS mCRC estimated the treatment benefit of Vectibix plus FOLFOX compared with FOLFAX alone on OS (Figure 3). Median OS among 325 patients with wild-type KRAS mCRC who received Vectibix plus FOLFAX was 23.8 months (95% CI: 20.0, 27.7) vs 18.4 months (95% CI: 17.4, 22.8) among 331 patients who received FOLFAX alone ( \text{HR} = 0.83, 95% \text{ CI: 0.70, 0.98} ). (See Figure 3) Retrospective exploratory analyses in the RAS wild-type subgroup Among the 656 patients with wild-type KRAS exon 2 mCRC, RAS mutation status was assessed for 620 patients using Sanger bidirectional sequencing and Surveyor®/WAVE® analysis. Of these 620 patients, approximately 17% of patients ( n = 104 ) tumors harbored mutations in KRAS exons 3 or 4 or in NRAS exons 2, 3, and 4. Retrospective subset analyses were then conducted within the subset of patients without RAS mutations ( n = 512 ) as described above. In the wild-type RAS subgroup, 85% of patients were men and 91% were White, 2% Black, and 5% Hispanic or Latino. Sixty-five percent of patients had colon cancer and 35% had rectal cancer. ECOG performance was 0 in 57% of patients, 1 in 37% of patients, and 2 in 6% of patients. Median age was 61 years. (See Table 6 and Figure 4) 14.3 RAS-Mutant mCRC Vectibix is not effective for the treatment of patients with RAS-mutant mCRC, defined as a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), or exon 4 (codons 117 and 146) of KRAS and NRAS. In Study 20050203, among patients with RAS-mutant tumors, the median PFS was 7.3 months (95% CI: 6.3, 7.9) among 272 patients receiving Vectibix plus FOLFAX and 8.7 months (95% CI: 7.6, 9.4) among patients who received FOLFAX alone ( \text{HR} = 1.31, 95% \text{ CI: 1.07, 1.60} ). The median OS was 15.6 months (95% CI: 13.4, 17.9) among patients receiving Vectibix plus FOLFAX and 19.2 months (95% CI: 16.7, 21.8) among patients who received FOLFAX alone ( \text{HR} = 1.24, 95% \text{ CI: 1.02, 1.55} ). In Study 20100007, among patients with RAS-mutant tumors, no differences in OS or PFS were observed between the treatment arms ( n = 54; \text{OS HR} = 0.99 (95% \text{ CI: 0.49, 2.00}); \text{PFS HR} = 1.03 (95% \text{ CI: 0.56, 1.90}) ). <strong>020987, 04/25/2019</strong> 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 4.9 hours in healthy subjects, they still have minimal accumulation (23% or less) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed. For known pediatric poor metabolizers, a dose reduction should be considered. 125511, 12/17/2018 Parathyroid Hormone Inborn Errors of Metabolism CASR Indications and Usage, Clinical Studies 1 INDICATIONS AND USAGE NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Limitations of Use: • Because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone [see Warnings and Precautions (5.1)]. • NATPARA was not studied in patients with hyperparathyroidism caused by calcium-sensing receptor mutations. • NATPARA was not studied in patients with acute post-surgical hypoparathyroidism. 14 CLINICAL STUDIES Study in Patients with Established Hypoparathyroidism (…) Patients with hypoparathyroidism due to calcium-sensing receptor mutations were excluded from the trial. (…)</td>
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| 021299, 01/04/2017 | Paroxetine | Psychiatry | CYP2D6 | Drug Interactions | **DRUG INTERACTIONS**  
(…). 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 in and 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. (…) |
| 210622, 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 transferrin 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, 05/31/2017 | Pazopanib (1) | Oncology | UGT1A1 | Clinical Pharmacology | **12 CLINICAL PHARMACOLOGY**  
12.5 Pharmacogenomics  
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 (NOI CTC Grade 2) occurred in 32% (42/133) of HLA-B*57:01 allele carriers and in 19% (38/2101) of non-carriers and ALT > 5 x ULN (NOI CTC 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)]. |
| 022465, 05/31/2017 | 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 (NOI CTC Grade 2) occurred in 32% (42/133) of HLA-B*57:01 allele carriers and in 19% (38/2101) of non-carriers and ALT > 5 x ULN (NOI CTC 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)]. |
| 103949, 01/08/2019 | Peginterferon Alfa-2b | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology | **12 CLINICAL PHARMACOLOGY**  
12.5 Pharmacogenomics  
(…) A retrospective genome-wide association analysis1,2 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 the (TA)6/(TA)7 genotypes. |
| 125203, 07/13/2018 | Pegloticase | Rheumatology | G6PD | Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information | **BOXED WARNING**  
**WARNING: ANAPHYLAXIS AND INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA**  
(…) Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency (4.5.3). |

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<td>Pembrolizumab (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (ipilimumab-Refractory Melanoma) The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. (...)</td>
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<td>125514, 06/17/2019</td>
<td>Pembrolizumab (2)</td>
<td>Oncology</td>
<td>CD274/ PD-L1</td>
<td>Indications and Usage, Dosage and Administration Clinical Studies</td>
<td>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 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. 1.4 Head and Neck Squamous Cell Cancer 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). 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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**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.

1.7 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test (see Dosage and Administration (2.1)), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

This indication is approved under accelerated approval based on tumor response rate and duration of response (see Clinical Studies (14.7)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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.

1.8 Gastric Cancer

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 durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.10 Cervical Cancer

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.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, or Cervical Cancer

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation (see Clinical Studies (14.2)).
- metastatic NSCLC (see Clinical Studies (14.2)), or in patients who have had prior treatment with platinum-containing chemotherapy and whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy (see Clinical Studies (14.7)).
- first-line treatment of metastatic or unresectable, recurrent HNSCC (see Clinical Studies (14.4)).
- metastatic urothelial carcinoma (see Clinical Studies (14.7)).
- metastatic gastric cancer (see Clinical Studies (14.9)). If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- recurrent or metastatic cervical cancer (see Clinical Studies (14.10)). Information on FDA-approved tests for the detection of PD-L1 expression for these indications is available at: [http://www.fda.gov/CompanionDiagnostic](http://www.fda.gov/CompanionDiagnostic).

### 14 CLINICAL STUDIES

#### 14.1 Melanoma

**Ipilimumab-Naive Melanoma**

(….) Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. (….) A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease, 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 BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. (….)

**Adjuvant Treatment of Resected Melanoma**

(…) The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually. The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (>4 positive lymph nodes); 50% were BRAF wild type and 44% were BRAF wild type and 44% had PD-L1 positive melanoma with TPS ≥1% according to an IUO assay. (….)

For patients with PD-L1 positive tumors, the HR was 0.54 (95% CI: 0.42; 0.69); p < 0.001. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

#### 14.2 Non-Small Cell Lung Cancer

**First-line treatment of metastatic non-small 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. Patients with autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or who had received 

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<td>more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS &lt;1% (negative) vs. TPS ≥1%). (…) (The study population characteristics: median age of 66 years (range: 34 to 84); 46% 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 &lt;1%. [See Table 21] (…)</td>
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<td>First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy. The efficacy of KEYTRUDA in combination with carboplatin and investigator’s choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407 (NCT02775439), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS &lt;1% (negative) vs. TPS ≥1%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). (…) (The study population characteristics were: median age of 66 years (range: 29 to 88); 56% age 65 or older; 81% male; 77% White; 71% ECOG performance status of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS &lt;1%; 16% were from the East Asian region; and 60% received paclitaxel. (…)</td>
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<td>First-line treatment of metastatic NSCLC as a single agent. The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220884), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. (…) Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥1% vs. TPS 1 to 49%). (…) (The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 32 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS 21%. [See Table 32] (…)</td>
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<td>The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≤50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11). [See Figure 6] (…)</td>
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<td>KEYNOTE-024 The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were eligible. (…)</td>
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<td>Previously treated NSCLC The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1023 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit. Patients had a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS 1-49%). ECOG performance status (0 vs. 1), and geographic region (East Asia vs. non-East Asia). (…) (The study population characteristics were: median age of 66 years (range: 20 to 88); 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG performance status 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. (…)</td>
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<td>14.4 Head and Neck Squamous Cell Cancer First-line treatment of metastatic or unresectable, recurrent HNSCC. The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 status (TPS &lt;1% [negative] vs. TPS ≥1%). (…) Randomization was stratified by age (65 or older vs. younger), histology (squamous cell vs. non-squamous cell), geographic region (East Asia vs. non-East Asia), and PD-L1 status (TPS &lt;1% [negative] vs. TPS ≥1%). (…) The study population characteristics were: median age of 66 years (range: 20 to 94); 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients’ tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 93% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients’ tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥2. (…)</td>
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<td>Pembrolizumab (3)</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies</td>
<td>statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. (…) In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥2 (HR 0.69, 95% CI: 0.51, 0.94).</td>
</tr>
</tbody>
</table>

14.7 Urothelial Carcinoma
Cisplatin Ineligible Patients with Urothelial Carcinoma
(…) Among the 370 patients, 30% (n = 110) had tumors that expressed PD-L1 with a combined positive score (CPS) of ≥ 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The study population characteristics of these 110 patients were: median age 73 years, 68% male, and 97% White. (See Table 41) (…) Previously Untreated Urothelial Carcinoma
KEYNOTE-361 (NCT02853305) is an ongoing, multicenter, randomized study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study compares KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. The trial also enrolled a third arm of monotherapy with KEYTRUDA to compare to platinum-based chemotherapy alone. The independent Data Monitoring Committee (IDMC) for the study conducted a review of early data and found that in patients classified as having low PD-L1 expression (CPS <10), those treated with KEYTRUDA monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The IDMC recommended to stop further accrual of patients with low PD-L1 expression in the monotherapy arm, however, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm. 14.8 Microsatellite Instability-High Cancer
See Table 30
14.9 Gastric Cancer
(…) Among the 269 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. (…) 14.10 Cervical Cancer
(…) 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 PD-L1 IHC 22C3 pharmDx Kit. (…) (…) No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 33 for patients with PD-L1 expression (CPS ≥1). (See Table 48) (…) 14.13 Renal Cell Carcinoma
The efficacy of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease requiring systemic immunosuppression within the last 2 years were ineligible. (…) (…) Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status. (…) 1 INDICATIONS AND USAGE
1.8 Microsatellite Instability-High Cancer
KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.6)]. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.
2 DOSAGE AND ADMINISTRATION
2.9 Recommended Dosage for MSI-H Cancer
The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression [see Clinical Studies (14.6)]. The recommended dose of KEYTRUDA in children is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. 8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of KEYTRUDA have been established in pediatric patients with cHL, PMBCL, and MSI-H cancer. Use of KEYTRUDA in pediatric patients with cHL, PMBCL, and MSI-H cancers is supported by evidence from adequate and well-controlled studies of KEYTRUDA in adults with additional pharmacokinetic and safety data in pediatric patients [see Adverse Reactions (6.1), Clinical Studies (14.4, 14.5, 14.7), Clinical Pharmacology (12.3)].
14 CLINICAL STUDIES
14.8 Microsatellite Instability-High Cancer
The efficacy of KEYTRUDA was evaluated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. (…) (See Table 43) |

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<td>Pembrolizumab (4)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>A total of 149 patients with MSI-H or dMMR cancers were identified across the five clinical trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety-eight percent of patients had non-squamous nonsmall cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, was 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.</td>
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</table>
| 125514, 06/17/2019 | Oncology | ALK | 1 INDICATIONS AND USAGE | The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905687), 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 6% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-containing regimen, 22% 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 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), active-controlled trial in 1251 patients with PD-L1 expressing 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 carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. (…)

Previously Treated NSCLC

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

14 CLINICAL STUDIES

14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy. The efficacy of KEYTRUDA was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 1016 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. (…)

First-line treatment of metastatic NSCLC as a single agent

KEYNOTE-042

The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were included. Patients were treated with KEYTRUDA 200 mg every 3 weeks with high PD-L1 tumor expression: 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology. 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 during the prior 26 weeks of initiation of study were ineligible. (…)

Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905687), 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% * Therapeutic areas do not necessarily reflect the CDER review division.
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<td>Perphenazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions, Clinical Pharmacology</td>
<td>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. (…)</td>
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| 125409, 12/18/2018                      | 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)]. |
|                                        |               |                   |            |                   | 2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics. 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. |
|                                        |               |                   |            |                   | 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. (…) Adjutant 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. (…) |
|                                        |               |                   |            |                   | 12 CLINICAL PHARMACOLOGY
12.6 Cardiac Electrophysiology The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in CLEOPATRA. No large changes in the mean QTc interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design. |
|                                        |               |                   |            |                   | 14 CLINICAL STUDIES
14.1 Metastatic Breast Cancer |

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<td>ESR, PGR</td>
<td>Clinical Studies</td>
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**Clinical Studies**

**14.1 Metastatic Breast Cancer**

(…) Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half 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. (…)

(…) Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.98 (95% CI: 0.61, 1.52). (…)

**14.2 Neoadjuvant Treatment of Breast Cancer**

NeoSphere

NeoSphere (NCT00545688) was a multicenter, randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab, or TRYPHAENA. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity.

**TRYPHENA**

An additional neoadjuvant study (TRYPHENA, NCT00796989) was conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. (…)

**BERENICE**

A two-arm non-randomized study (BERENICE, NCT02132489) 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. (…)

**14.3 Adjuvant Treatment of Breast Cancer**

APHINITY (NCT01588771) was a multinational, randomized, double-blind, placebo-controlled study conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. (…)

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PHARMACODYNAMICS

Phenytoin is primarily metabolized by the liver and eliminated in the urine. The primary metabolite is 5-epiphenytoin. The plasma clearance of phenytoin is inversely related to body weight and directly related to serum levels.

CLINICAL PHARMACOLOGY

1. Pharmacokinetics

Phenytoin is rapidly absorbed following oral administration. The time to achieve peak plasma concentrations ranges from 0.5 to 2 hours. The bioavailability of phenytoin is approximately 90%.

2. Pharmacodynamics

Phenytoin is a competitive inhibitor of the sodium channel, leading to a decrease in the amplitude and duration of action potentials. It also inhibits the release of neurotransmitters and reduces excitability of central and peripheral neurons.

3. Precautions

- Renal Function
  - In patients with impaired renal function, the dosage of phenytoin may need to be adjusted to prevent toxicity.

- Pregnancy
  - Phenytoin may cause adverse effects in the offspring. Pregnant women should be informed of the potential risks.

- Lactation
  - Phenytoin is excreted in breast milk. Mothers who are breastfeeding should be informed of the potential risk to the infant.

- Children
  - The pharmacokinetics of phenytoin may be different in children compared to adults.

4. Interactions

- CYP2C9
  - Phenytoin is a substrate of CYP2C9. Co-administration of drugs that are inhibitors or inducers of CYP2C9 may affect the plasma concentrations of phenytoin.

- HLA-B*1502
  - Studies have shown an association between the presence of HLA-B*1502 and the risk of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

5. Preparations

- Oral
  - Phenytoin is available in oral tablets, capsules, and suspensions.

- Parenteral
  - Phenytoin is available for intravenous administration.

- Parenteral

ADVERSE REACTIONS

1. Neurological

Phenytoin may cause adverse effects on the nervous system, including dizziness, headache, ataxia, and seizures.

2. Skin

Phenytoin may cause skin reactions such as rash, itching, and hives.

3. Other

Phenytoin may cause gastrointestinal effects such as nausea, vomiting, and diarrhea.

CONTRAINDICATIONS

Phenytoin is contraindicated in patients with a history of hypersensitivity reactions to phenytoin.

WARNING

- Serious Dermatologic Reactions
  - Patients should be monitored for the development of skin reactions and promptly discontinued if they occur.

- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
  - Patients should be monitored for the development of these conditions and promptly discontinued if they occur.

- Monitoring

- Serum Phenytoin Levels
  - Patients should have their phenytoin serum levels monitored to ensure therapeutic levels are achieved.

- Electrocardiogram (ECG)
  - ECGs should be performed periodically to monitor for cardiac effects.

NOCUMBER 010151, 06/16/2016

Phenytoin (1)

Phenytoin (2)

Phenytoin (3)

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<tr>
<td>010151, 06/16/2016</td>
<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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<tr>
<td>010151, 06/16/2016</td>
<td>Phenytoin (2)</td>
<td>Neurology</td>
<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>
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<tr>
<td>010151, 06/16/2016</td>
<td>Phenytoin (3)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings</td>
<td>PHARMACODYNAMICS</td>
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</table>
| 203469, 10/18/2018 | Ponatinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | (…) Higher systemic exposure of piroxicam has been noted in subjects with CYP2C9 polymorphisms compared to normal metabolizer type subjects [see Clinical Pharmacology (12.5)].

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/2 (n=9), heterozygous CYP2C9*1/3 (n=9), and homozygous CYP2C9*3/3 (n=1) genotypes showed 5.7-, 5.7-, and 5.7-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/1 (n=17, normal metabolizer genotype) following administration of a single oral dose. The mean elimination half-life values of piroxicam for subjects with CYP2C9*1/3 (n=9) and CYP2C9*3/3 (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with CYP2C9*1/1 (n=17). It is estimated that the frequency of the homozygous*3 genotype is 5% to 1% in the population at large; however, frequencies as high as 5.7% have been reported in certain ethnic groups.

Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance.

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</thead>
</table>
| 022307, 03/28/2019               | Prasugrel (1) | Cardiology       | CYP2C19   | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 8 USE IN SPECIFIC POPULATIONS  
8.9 Metabolic Status  
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.  
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 prodrugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced metabolizers. (…) |
| 022307, 03/28/2019               | Prasugrel (2) | Cardiology       | CYP2C9    | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 8 USE IN SPECIFIC POPULATIONS  
8.9 Metabolic Status  
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.  
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  
|
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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<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>(…) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…)</td>
</tr>
<tr>
<td>022307, 03/28/2019</td>
<td>Prasugrel (4)</td>
<td>Cardiology</td>
<td>CYP2B6</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>(…) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…)</td>
</tr>
<tr>
<td>008316, 06/22/2017</td>
<td>Primaquine (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage</td>
<td>CONTRAINDICATIONS: Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings).</td>
</tr>
</tbody>
</table>

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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
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<tr>
<td>06/2019</td>
<td></td>
<td></td>
<td></td>
<td>Pharmacology, Clinical Reactions, Precautions, Warnings and Administration</td>
<td></td>
</tr>
<tr>
<td>11/02/2018</td>
<td>021416, 020545</td>
<td>CYP2D6</td>
<td>Nonspecific</td>
<td>ADVERSE REACTIONS</td>
<td></td>
</tr>
<tr>
<td>007898</td>
<td></td>
<td></td>
<td></td>
<td>Leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.</td>
<td></td>
</tr>
<tr>
<td>020545</td>
<td></td>
<td></td>
<td></td>
<td>OVERDOSE</td>
<td></td>
</tr>
<tr>
<td>021416, 11/02/2018</td>
<td></td>
<td></td>
<td></td>
<td>Symptoms of overdosage of primaquine phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia, and anemia. The most striking symptoms are granulocytopenia and acute hemolytic anemia in G6PD deficient patients. Acute hemolysis occurs, but patients recover completely if the dosage is discontinued.</td>
<td></td>
</tr>
</tbody>
</table>

### Pharmacogenomic Biomarkers

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<tr>
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<td>Infectious Diseases</td>
<td>CYP2B6</td>
<td>ADVERSE REACTIONS</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>ADVERSE REACTIONS</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>ADVERSE REACTIONS</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>DOSAGE AND ADMINISTRATION</td>
</tr>
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<td>Warnings and Precautions</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>DRUG INTERACTIONS</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>CLINICAL PHARMACOLOGY</td>
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</tbody>
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<tbody>
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<td>021438, 11/19/2013</td>
<td>Propranolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
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<tr>
<td>073644, 07/17/2014</td>
<td>Protriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
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<tr>
<td>089338, 02/02/2010</td>
<td>Quinidine</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Precautions</td>
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<tr>
<td>021799, 06/19/2019</td>
<td>Quinine Sulfate (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
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<tr>
<td>021799, 06/19/2019</td>
<td>Quinine Sulfate (2)</td>
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<td>Drug Interactions</td>
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<tr>
<td>020973, 06/07/2018</td>
<td>Rabeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions</td>
</tr>
</tbody>
</table>

Other drugs such as encaaine, metoprol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylproprafenone 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 650 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxilation 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-hydroxymetabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The larger inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity [see Dosage and Administration (2)].

Inter-Subject Variability

With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and nonlinear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability was observed following both single and multiple dose administration of RYTHMOL SR capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.

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<tr>
<td>020815, 06/27/2018</td>
<td>Ramucirumab (2)</td>
<td>Oncology</td>
<td>UGT1A1 Polymorphism</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.2 Non-Small Cell Lung Cancer</td>
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<td></td>
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<td>(…) Clinical studies were conducted in patients with locally advanced or metastatic non-small cell lung cancer who had progression after standard chemotherapy. In a study comparing 250 mg of ramucirumab with placebo, the median progression-free survival was 5.0 months for patients with the <em>UGT1A1</em> 28/28 genotype (59% of patients) and 2.6 months for patients with the <em>UGT1A1</em> 28/*28 genotype (41% of patients). In a study comparing 750 mg of ramucirumab with placebo, the median progression-free survival was 5.0 months for patients with the <em>UGT1A1</em> 28/28 genotype (52% of patients) and 2.6 months for patients with the <em>UGT1A1</em> 28/*28 genotype (48% of patients). (See Table 8)</td>
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<tr>
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<td>Infectious Diseases</td>
<td>EGFR</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Phamacogenomics</td>
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<td></td>
<td>UGT1A1 Polymorphism</td>
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<td></td>
<td>There is no evidence that common <em>UGT1A1</em> polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult subjects with <em>UGT1A1</em> 28/28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09). In the neonatal study IMPAACT P1110, there was no association between apparent clearance (CL/F) of raltegravir and UGT 1A1 genotype polymorphisms. (…)</td>
</tr>
<tr>
<td>022145, 03/05/2018</td>
<td>Raltegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>125477, 08/14/2018</td>
<td>Ramucirumab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<tr>
<td>125477, 08/14/2018</td>
<td>Ramucirumab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Clinical Studies</td>
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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
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</table>
| 103946, 09/14/2017                      | Rasburicase (1) | Oncology | G6PD | Boxed Warning, Contraindications, Warnings and Precautions | BOXED WARNING

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

Hemolysis

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.2 Hemolysis

Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in <1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Boxed Warning, Contraindications (4.5)].

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<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 103946, 09/14/2017                      | Rasburicase (2) | Oncology | CYB5R | Boxed Warning, Contraindications, Warnings and Precautions | BOXED WARNING

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

Methemoglobinemia

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.3 Methemoglobinemia

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

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</table>
| 203066, 06/14/2018                      | Regorafenib | Oncology | RAS | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

STIVARGA is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wildtype, an anti-EGFR therapy.

14 CLINICAL STUDIES

14.1 Colorectal Cancer

(…) Baseline demographics were: median age 61 years, 61% men, 78% White, and all patients had an ECOG performance status of 0 or 1. The primary sites of disease were colon (65%), rectum (29%), or both (6%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutation/negative tumors received prior bevacizumab as a single agent or combination therapy. (…)

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<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 209092, 07/18/2018                      | Ribociclib (1) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE

KISQALI is indicated in combination with:

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

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

6 ADVERSE REACTIONS

MONALEESA-2: KISQALI in combination with Letrozole

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

The safety data reported below are based on MONALEESA-2, a clinical study of 686 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for >12 months. (…)

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† 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 “Non-specific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.
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### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2019**

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<th>Labeling Text‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>209092, 07/18/2018</td>
<td>Ribociclib (2)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>MONALEESA-7: KISQALI in combination with an Aromatase Inhibitor Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a non-steroidal aromatase inhibitors (NSAI) or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. (…) MONALEESA-3: KISQALI in combination with Fulvestrant Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. (…)</td>
</tr>
</tbody>
</table>

**14 CLINICAL STUDIES**

**MONALEESA-2: KISQALI in Combination with Letrozole**

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy MONALEESA-2 was a randomized, double-blind, placebo-controlled, multicenter clinical study of KISQALI plus letrozole versus placebo plus letrozole conducted in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. (…) MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy MONALEESA-7 was a randomized, double-blind, placebo-controlled study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease. (…) MONALEESA-3: KISQALI in Combination with Fulvestrant Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy MONALEESA-3 was a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…) |

**1 INDICATIONS AND USAGE**

KISQALI is indicated in combination with:
- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy, or fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

**6 ADVERSE REACTIONS**

MONALEESA-2: KISQALI in combination with Letrozole Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy The safety data reported below are based on MONALEESA-2, a clinical study of 688 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months. (…) MONALEESA-7: KISQALI in combination with an Aromatase Inhibitor Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a non-steroidal aromatase inhibitors (NSAI) or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. (…) MONALEESA-3: KISQALI in combination with Fulvestrant Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. (…) |

**14 CLINICAL STUDIES**

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<th>Therapeutic Area$^*$</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text$^‡$</th>
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</thead>
</table>
| 00272, 01/25/2019                      | Risperidone | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics  
Absorption  
Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=10%) when compared to a solution.  
Pharmacokinetic studies showed that RISPERDAL M-TAB Orally Disintegrating Tablets and RISPERDAL Oral Solution are bioequivalent to RISPERDAL Tablets.  
Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosage range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers.  
Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).  
Metabolism  
(….) CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers. Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone ([see Drug Interactions (7)]). This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. These 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 30 hours. |

| 103705, 01/25/2019 | Rituximab | Oncology | MS4A1 (CD20 antigen) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | MONALEESA-3 was a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…) |

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<tbody>
<tr>
<td>02/24/06, 01/15/2019</td>
<td>Rivaroxaban</td>
<td>Cardiology</td>
<td>F5 (Factor V Leiden)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<tr>
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<td></td>
<td>14.3 Reduction in the Risk of Recurrence of DVT and/or PE</td>
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<td></td>
<td>EINSTEIN CHOICE Study</td>
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<td>(…) A total of 2275 patients were randomized and followed on study treatment for a mean of 290 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 idopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophilic conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%). (…)</td>
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<tr>
<td>02/05/33, 11/02/2018</td>
<td>Ropivacaine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia</td>
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<td>Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6- phosphate dehydrogenase deficiency, congenital or idopathic 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>02/05/33, 11/02/2018</td>
<td>Ropivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia</td>
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<td>02/13/06, 11/09/2018</td>
<td>Rosuvastatin</td>
<td>Endocrinology</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>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 52T &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>
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<tr>
<td>209115, 04/06/2018</td>
<td>Rucaparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
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<td></td>
<td>1.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies</td>
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<td>Rubraca is indicated for the treatment of adult patients with 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)].</td>
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<td></td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.3 Patient Selection for Treatment of BRCA-mutated Ovarian Cancer</td>
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</thead>
<tbody>
<tr>
<td>Rucaparib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>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 Indications and Usage (1.2) and Clinical Studies (14.2)]. 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>.</td>
</tr>
<tr>
<td>Rucaparib (3)</td>
<td>Oncology</td>
<td>CYP1A2</td>
<td>Clinical Pharmacology</td>
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<tr>
<td>Rucaparib (4)</td>
<td>Oncology</td>
<td>Homologous Recombination Deficiency</td>
<td>Clinical Studies</td>
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020478, 04/27/2017
Sevoflurane  Anesthesiology  RYR1  Warnings  

**WARNINGS**

Malignant Hyperthermia In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as genically susceptible individuals, such as those with inherited hyperadrenergic 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-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C [cytosine] to T [thymine] substitution) is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor. Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with OLYSIO-containing regimens. (See Table 12 and 13)

14 CLINICAL STUDIES

14.2 OLYSIO in Combination with Sofosbuvir

Adult Subjects with HCV Genotype 1 Infection

(…) These 59 subjects had a median age of 57 years (range 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, and 24% Black or African American; 46% had a BMI greater than or equal to 30 kg/m2; the median baseline HCV RNA level was 6.75 log10 IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0, F2 and F3, respectively, and 25% had HCV genotype 1a of which 41% carried Q80K at baseline, and 25% had HCV genotype 1b; 14% had IL28B CC genotype, 64% IL28B CT genotype, and 22% IL28B TT genotype; 75% were prior null responders to Peg-IFN-alfa and RBV, and 25% were treatment-naive.

OPTIMIST-1 was an open-label, randomized Phase 3 trial in HCV genotype 1-infected subjects without cirrhosis who were treatment-naive or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred fifty-five subjects received 12 weeks of OLYSIO with sofosbuvir. The 155 subjects without cirrhosis receiving 12 weeks of OLYSIO with sofosbuvir had a median age of 56 years (range 19 to 70 years; with 7% above 65 years); 53% were male; 76% were White, 20% Black or African American, and 16% Hispanic; 37% had a BMI of >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 26% had HCV genotype 1b; 26% had IL28B CC genotype, 55% IL28B CT genotype, and 74% 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 Q80K carriers: treatment-naive and treatment-experienced (91/116 [79%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%], and subjects with IL28B CC and non-CC genotypes (43/43 [100%] and 107/112 [96%], respectively).

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

Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection

(…) In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the OLYSIO and placebo treatment groups. 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 800,000 IU/mL; 74% had METAVIR fibrosis score F0, F1 or F2; 16% METAVIR fibrosis score F3, and 10% METAVIR fibrosis score F4 (cirrhosis); 48% had HCV genotype 1a; 51% HCV genotype 1b; 29% had IL28B CT genotype, 56% IL28B CT genotype, and 15% IL28B TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a 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-NAïve East Asian Subjects with HCV Genotype 1 Infection

(…) These 304 subjects had a median age of 45 years (range: 18 to 68 years; with 2% above 65 years); 49% were male; all were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater or equal to 30 kg/m2; 84% had baseline HCV RNA levels greater than 800,000 IU/mL.
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</thead>
</table>
| Siponimod | Neurology | CYP2C9 | Dosage and Administration, Contraindications, Drug Interactions, Use in Specific Populations, Clinical Pharmacology | **2 DOSEAGE 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), and Use in Specific Populations (8.6)). An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available.  
**2.2 Recommended Dosage in Patients With CYP2C9 Genotypes †1/*1, †1/*2, or †2/*2**  
Maintenance Dosage  
After treatment titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 2 mg taken orally once daily starting on Day 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 (5.5)). 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)  
If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.  
**2.3 Recommended Dosage in Patients With CYP2C9 Genotypes †1/*3 or †2/*3**  
Maintenance Dosage  
In patients with a CYP2C9 †1/*3 or †2/*3 genotype, after treatment titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 5.  
**Treatment Initiation**  
Initiate MAYZENT with a 4-day titration, as shown in Table 2 (see Warnings and Precautions (5.5) 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) |

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| If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen. |

### 4 CONTRAINDICATIONS

MAYZENT is contraindicated in patients who have:

- A CYP2C9*3/*3 genotype [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)] (…)

### 7 DRUG INTERACTIONS

#### 7.6 CYP2C9 and CYP3A4 Inducers

Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer. Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and*2/*3 genotypes [see Clinical Pharmacology (12.3)].

#### 8 USE IN SPECIFIC POPULATIONS

#### 8.6 CYP2C9 Genotype

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

#### 12 CLINICAL PHARMACOLOGY

##### 12.2 Pharmacokinetics

Siponimod as an Object of Interaction

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

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 AUCtau,ss of siponimod across different CYP2C9 genotypes, according to in silico evaluation [see Drug Interactions (7.5)].

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 AUCtau,ss and Cmax,ss by 57% and 45%, respectively in CYP2C9*1/*1 subjects. Rifampin and efavirenz (moderate CYP3A4 inducer) reduced the AUCtau,ss of siponimod by up to 78% and up to 52%, respectively, across CYP2C9 genotypes, according to in silico evaluation [see Drug Interactions (7.6)].

Oral Contraceptives

The effects of coadministration of siponimod 2 mg and 4 mg (twice the recommended dosage) once daily with a monophasic oral contraceptive (OC) containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were assessed in 24 healthy female subjects (18 to 40 years of age; CYP2C9*1/*1 genotype). There were no clinically relevant effects on the PK or PD of the OC. No interaction studies have been performed with OCs containing other progestagens; however, an effect of siponimod on their exposure is not expected.

##### 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- to 4-fold higher in CYP2C9*2/*3 and CYP2C9*3/*3 genotypes, 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 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were assessed in 24 healthy female subjects (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.

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- to 4-fold higher in CYP2C9*2/*3 and CYP2C9*3/*3 genotypes, 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. CI/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, 81, 91, and 285% higher in CYP2C9*2/*3, CYP2C9*3/*3, and CYP2C9*2/*3 genotypes respectively.

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<tbody>
<tr>
<td>203922, 10/19/2017</td>
<td>Sodium Nitrite (1)</td>
<td>Toxicology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<tr>
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<td>5.6 G6PD Deficiency</td>
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<td>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.</td>
</tr>
<tr>
<td></td>
<td>Sodium Nitrite (2)</td>
<td>Toxicology</td>
<td>Nonspecific Congenital Methemoglobinemia</td>
<td>Boxed Warning, Warnings and Precautions</td>
<td>BOXED WARNING</td>
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<td></td>
<td>WARNING: LIFE THREATENING HYPOTENSION AND METHEMOglobIN FORMATION</td>
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<td>Sodium nitrite can cause serious adverse reactions and death in humans, even at doses less than twice the recommended therapeutic dose. Sodium nitrite causes hypotension and methemoglobin formation, which diminishes oxygen carrying capacity. Hypotension and methemoglobin formation can occur concurrently or separately. Because of these risks, sodium nitrite should be used to treat acute life-threatening cyanide poisoning and be used with caution in patients where the diagnosis of cyanide poisoning is uncertain. Patients should be closely monitored to ensure adequate perfusion and oxygenation during treatment with sodium nitrite. Alternative therapeutic approaches should be considered in patients known to have diminished oxygen or cardiovascular reserve (e.g., smoke inhalation victims, pre-existing anemia, cardiac or respiratory compromise), and those at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency) as 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)]</td>
</tr>
<tr>
<td>020572, 03/31/2009</td>
<td>Sodium Phenybutyrate</td>
<td>Inborn Errors of Metabolism</td>
<td>ASS1, CPS1, OTC (Urea Cycle Disorders)</td>
<td>Indications and Usage, Dosage and Administration</td>
<td>INDICATIONS AND USAGE</td>
</tr>
</tbody>
</table>
|                                        |                     |                   |            |                   | 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 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 hyperammoninemia 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% (47/87 patients tested). (…) (…) In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemia encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98%. (…) |
|                                        |                     |                   |            |                   | 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 9–13.0 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 |
|                                        |                     |                   |            |                   | (…) At the recommended dose of sodium phenylbutyrate, it is suggested that infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period. Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake. From 4 months to 1 year of age, it is recommended that the infant receive at least 1.4 g/kg/day, but 1.7 g/kg/day is advisable. From 1 to 3 years of age, the protein intake should not be less than 1.2 g/kg/day; 1.4 g/kg/day is advisable during this period. For neonatal-onset patients with carbamylphosphate synthetase deficiency or ornithine transcarbamylase deficiency who are at least 6 months of age, it is recommended that the daily protein intake be equally divided between natural protein and supplemental essential amino acids. |

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<td>204671, 10/23/2018</td>
<td>Sofosbuvir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>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 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.</td>
</tr>
<tr>
<td>208341, 11/06/2017</td>
<td>Sofosbuvir and Velpatasvir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14.4 Clinical Trials in Subjects Coinfected with 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 89% (24/26) in subjects with baseline IL28B C/C allele and 75% (62/82) in subjects with baseline IL28B non-C/C alleles. (…) 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 (92%) 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.</td>
</tr>
</tbody>
</table>

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</table>
| 209195, 11/09/2017                      | Sofosbuvir, Velpatasvir, Voxlaptrevi | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | CLINICAL STUDIES
14.2 Clinical Trials in HCV DAA-Experienced Subjects
NS5A Inhibitor-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis (POLARIS-1)
(...)
14.3 Clinical Trials in HCV DAA-Experienced Adults With Cirrhosis (POLARIS-2)
NS5A Inhibitor-Experienced Adults With Cirrhosis (POLARIS-2)
(...)
14.4 Clinical Trials in HCV DAA-Experienced Adults With Decompensated Cirrhosis (POLARIS-3)
NS5A Inhibitor-Experienced Adults With Decompensated Cirrhosis (POLARIS-3)
(...)
14.5 Clinical Trials in HCV DAA-Experienced Adults With Compensated Cirrhosis Who Had Not Received An NS5A Inhibitor (POLARIS-4)
NS5A Inhibitor-Experienced Adults With Compensated Cirrhosis Who Had Not Received An NS5A Inhibitor (POLARIS-4)
(...)
14.6 Clinical Trials in HCV DAA-Inexperienced Adults With Cirrhosis (C 168992)
HCV DAA-Inexperienced Adults With Cirrhosis (C 168992)
(...) |
| 019998, 10/02/2018                     | Succimer | Hematology | G6PD | Clinical Pharmacology | CLINICAL PHARMACOLOGY
(...)
In addition to the controlled studies, approximately 250 patients with lead poisoning have been treated with succimer either orally or parenterally in open U.S. and foreign studies with similar results reported. Succimer has been used for the treatment of lead poisoning in one patient with sickle cell anemia and in five patients with glucose-6-phosphohydrogenase (G6PD) deficiency without adverse reactions. (…)

006453, 07/26/2018                  | Succinylcholine | Anesthesiology | BCHE | Warnings, Precautions | WARNINGS
(...)
Succinylcholine is metabolized by plasma cholinesterase and should be used with caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.

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

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

017731, 08/01/2016                | Sulfadiazine | Infectious Diseases | G6PD | Warnings | WARNINGS
(...)
The use of SILVADENE Cream 1% (silver sulfadiazine) in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur.

017777, 07/16/2014                | Sulfamethoxazole and Trimethoprim (1) | Infectious Diseases | G6PD | Precautions | PRECAUTIONS
Hemolysis in glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see Clinical Pharmacology and Dosage and Administration).

017377, 07/16/2014                | Sulfamethoxazole and Trimethoprim (2) | Infectious Diseases | Nonspecific (NAT) | Precautions | PRECAUTIONS
Electrolyte Abnormalities
(...)
During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are “slow acetylators” may be more prone to idiosyncratic reactions to sulfonamides. (…)

00707, 03/04/2014                 | Sulfasalazine (1) | Gastroenterology | G6PD | Precautions | PRECAUTIONS
General
AZULFIDINE EN-tabs Tablets should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, AZULFIDINE EN-tabs should be discontinued immediately.

00707, 03/04/2014                 | Sulfasalazine (2) | Gastroenterology | Nonspecific (NAT) | Clinical Pharmacology | CLINICAL PHARMACOLOGY
Pharmacokinetics
Metabolism: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to 5-hydroxysulfapyridine (SPOH) and N-acetyl-5-hydroxysulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-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; * Therapeutic areas do not necessarily reflect the CDER review division.
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<tr>
<td>211996, 05/03/2019</td>
<td>Tafamidis</td>
<td>Cardiology</td>
<td>12.1 TTR</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12. CLINICAL PHARMAOCOLOGY</td>
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<td>A proprietary TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer ex vivo. The TTR stabilization assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre- and post-treatment with 2-day in vitro denaturation with urea. Using this proprietary assay, a dose-dependent trend for greater TTR tetramer stabilization is observed for VYNDAQEL 80-mg compared to VYNDAQEL 20-mg. However, the clinical relevance of a higher TTR tetramer stabilization towards cardiovascular outcomes is not known. VYNDAQEL stabilized both the wild type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilized the TTR tetramer for 25 variants tested ex vivo. (…)</td>
</tr>
<tr>
<td>210607, 08/08/2018</td>
<td>Tafenoquine</td>
<td>Infectious Diseases</td>
<td>12.2 G6PD</td>
<td>Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
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<td>2.1 Tests to be Performed Prior to ARAKODA Dose Initiation</td>
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<td>All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA [see Contraindications (4), Warnings and Precautions (5.1)].</td>
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<td>4 CONTRAINDICATIONS</td>
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<td></td>
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<td>ARAKODA is contraindicated in:</td>
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<td>• patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia [see Warnings and Precautions (5.2)].</td>
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<td>• breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown [see Warnings and Precautions (5.3), Use in Specific Populations (8.2)].</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1. Hemolytic Anemia</td>
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<td>Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA [see Contraindications (4)]. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolysis should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status [see Contraindications (4)]. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients [see Adverse Reactions (6.1)]. Monitor patients for clinical signs or symptoms of hemolysis [see Warnings and Precautions (5.6)]. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur.</td>
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<td>5.2 G6PD Deficiency in Pregnancy and Lactation</td>
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<td>Potential Harm to the Fetus</td>
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<td>The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Use in Specific Populations (8.1 and 8.3)].</td>
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<td>Potential Harm to the Breastfeeding Infant</td>
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<td>A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeuling women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown [see Contraindications (4)]. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose [see Use in Specific Populations (8.2)].</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.1 Pregnancy Risk Summary</td>
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</tbody>
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<th>Labeling Text</th>
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</table>
| 211651, 10/16/2018                     | Talazoparib (1) | Oncology | BRCA       | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | 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)]. Inform the patient 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 urine or blood in their stools as these may be signs of hemolysis or methemoglobinemia (see Warnings and Precautions (5.1)]. The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (n=286) or a chemotherapy agent (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. (…)

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

**Treatment of gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer**

**EMBRACA**

The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg or healthcare provider’s choice of chemotherapy (cabazitaxel, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. (…)

14 CLINICAL STUDIES

**EMBRACA Study (NCT01945775)**

Deleterious or Suspected Deleterious Germline BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer

EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive TALZENNA 1 mg or healthcare provider’s choice of chemotherapy (cabazitaxel, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (TRAMBB1C versus non-TRAMBB1C), and history of central nervous system (CNS) metastasis (yes versus no). (…)

**Contraindication**

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.

**Use in Specific Populations**

**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 urine or blood in their stools as these may be signs of hemolysis or methemoglobinemia (see Warnings and Precautions (5.1)]. The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (n=286) or a chemotherapy agent (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. (…)

**1 INDICATIONS AND USAGE**

**TALZENNA** is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA (see Dosage and Administration (2.1)].

**2 DOSAGE AND ADMINISTRATION**

**2.1 Patient Selection**

Select patients for the treatment of advanced breast cancer with TALZENNA based on the presence of germline BRCA mutations (see Indications and Usage (1)], Clinical Studies (14)]. Information on the FDA-approved test for the detection of BRCA mutations is available at [http://www.fda.gov/companiondiagnostics](http://www.fda.gov/companiondiagnostics).
Table of Pharmacogenomic Biomarkers in Drug Labeling

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<td>Reactions, Clinical Studies</td>
<td>TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Selected patients for therapy based on an FDA-approved companion diagnostic for TALZENNA (see Dosage and Administration (2.1)).</td>
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<td>6 ADVERSE REACTIONS</td>
<td>6.1 Clinical Trials Experience Treatment of gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer</td>
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<td>EMBRACA</td>
<td>The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (n=206) or a chemotherapy agent (capecitabine, erubulin, gemcitabine, or vinorelbine) of the healthcare provider’s choice (n=126) until disease progression or unacceptable toxicity. (…)</td>
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<td>EMBRACA Study (NCT01945775)</td>
<td>Deleterious or Suspected Deleterious Germline BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer</td>
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<td>EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive TALZENNA 1 mg or healthcare provider’s choice of chemotherapy (capecitabine, erubulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system (CNS) metastasis (yes versus no). (…)</td>
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<tr>
<td>021807, 04/08/2019</td>
<td>Tamoxifen (1)</td>
<td>Oncology</td>
<td>ESR, PGR</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>(Hormone Receptor)</td>
<td>SOLTAMOX is indicated for the treatment of adult patients with estrogen receptor-positive metastatic breast cancer.</td>
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<td>1.1 Metastatic Breast Cancer</td>
<td>SOLTAMOX is indicated:</td>
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<td>1.2 Adjuvant Treatment of Breast Cancer</td>
<td>• for the adjuvant treatment of adult patients with early stage estrogen receptor-positive breast cancer</td>
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<td>• to reduce the occurrence of contralateral breast cancer in adult patients when used as adjuvant therapy for the treatment of breast cancer.</td>
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<td>6 ADVERSE REACTIONS</td>
<td>6.1 Clinical Trials Experience Anastrozole Adjuvant Trial (ATAC: Aromide, Tamoxifen, Alone or in Combination) – Study of Anastrozole Compared to Tamoxifen for Adjuvant Treatment of Early Breast Cancer</td>
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<td>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 receptorpositive 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>12 CLINICAL PHARMACOGENOMICS</td>
<td>12.5 Pharmacogenomics The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women’s Health Eating and Living) Study (NCT00037877), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p=0.0011), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.</td>
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<td>14 CLINICAL STUDIES</td>
<td>14.2 Adjuvant Treatment of Breast Cancer Pooled Studies of Adjuvant Treatment of Breast Cancer</td>
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<td>The Early Breast Cancer Trials Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, 1995, 1998 and 2011. The 10-year outcome data were reported in 1998 for 36,689 women in 55 randomized trials of another formulation of adjuvant tamoxifen using doses of 20 to 40 mg per day for 1 to 5+ years. Twenty-five percent of patients received 1 year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Forty-eight percent of tumors were estrogen receptor (ER)-positive (&gt;10 fmol/mg), 21% were ER-poor (&lt;10 fmol/mg), and 31% were ER-unknown. Among 29,441 patients with ER-positive or ER-unknown breast cancer, 58% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node-positive disease and 46% had node-negative disease.</td>
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<td>in women with ER-positive or ER-unknown breast cancer:</td>
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<td>• With positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for tamoxifen vs. 50.5% for control (log-rank 2p &lt;0.00001). The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (log-rank 2p &lt;0.00001).</td>
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<tr>
<td>Oncology</td>
<td>F5</td>
<td>Warnings and Precautions</td>
<td>• With negative nodes who received at least 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (log-rank 2p &lt;0.0001). The recurrence-free rate at 10 years was 79.2% for tamoxifen vs. 64.3% for control (log-rank 2p &lt;0.00001).</td>
</tr>
<tr>
<td>Oncology</td>
<td>F2</td>
<td>Warnings and Precautions</td>
<td>• Who received 1 year or less, 2 years, or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17%, and 26%, respectively (2p &lt;0.0003). The corresponding reductions in breast cancer recurrence were 21%, 29%, and 47% (2p &lt;0.00001).</td>
</tr>
<tr>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>• Results in patients with ER-negative breast cancer</td>
</tr>
</tbody>
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<tr>
<td>020679, 01/23/2019</td>
<td>Tamsulosin</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Adverse Interactions, Clinical Pharmacology</td>
<td>The impact of CYP2D6 polymorphisms on the efficacy of tamsulosin is not well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or non-fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHI (Women’s Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (0.8) ng/mL in 27 ultra-rapid, 1,091 normal, 164 intermediate and 62 poor metabolizers (p&lt;0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.</td>
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<tr>
<td>201917, 10/28/2013</td>
<td>Telaprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR). rs12979860 was genotyped in 454 of 1088 subjects in Trial 108 (treatment-naïve) and 527 of 662 subjects in Trial C216 (previously treated) [see Clinical Studies (14.2 and 14.3) for trial descriptions]. SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naïve subjects receiving PR48 (Table 9). Among both treatment-naïve and previous treatment failures, subjects of all IL28B genotypes appeared to have higher SVR rates with regimens containing INCIVEX. 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)</td>
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<tr>
<td>021894, 09/13/2017</td>
<td>Tetrabenazine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Use in Specific Populations, 2 DOSAGE AND ADMINISTRATION 2.2 Individualization of Dose Dosing Recommendations Above 50 mg per day Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. Extensive and Intermediate CYP2D6 Metabolizers</td>
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| 05/23/2018, 012429, NDA/ANDA/BLA       | Thioguanine (1) | Oncology       | TPMT      | Dosage and Administration, Warnings, Precautions, Clinical Pharmacology | Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a divided twice-a-day regimen. The maximum recommended daily dose is 37.5 mg. If adverse reactions such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., anticholinergics) (see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

**Poor CYP2D6 Metabolizers**

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

**5 WARNINGS AND PRECAUTIONS**

5.3 Laboratory Tests

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

Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient’s CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 30 mg and the maximum recommended single dose is 25 mg (see Dosage and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

**8 USE IN SPECIFIC POPULATIONS**

8.7 Poor or Extensive CYP2D6 Metabolizers

Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as either poor (PMs) or extensive metabolizers (EMs) (see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)).

**Poor Metabolizers**

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

**Extensive / Intermediate Metabolizers**

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

**12 CLINICAL PHARMACOLOGY**

12.3 Pharmacokinetics

**Specific Populations**

Poor CYP2D6 Metabolizers

Although the pharmacokinetics of XENAZINE and its metabolites in patients who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively) (see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.7)).

**12.3.1 Pharmacokinetics**

**Specific Populations**

Poor CYP2D6 Metabolizers

Although the pharmacokinetics of XENAZINE and its metabolites in patients who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively) (see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.7)).

**Dosage and Administration**

(1) Patients with homozgyous deficiency of either TPMT or NUDT15 enzyme typically require 10% or less of the standard thioguanine dosage. Reduce initial dosage in patients who are known to have homozgyous TPMT or NUDT15 deficiency. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine dosages, 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**

(2) Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotype or phenotype (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozgyous 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**

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<td>Tipiracil and Trifluridine (1)</td>
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<td>ERBB2 (HER2)</td>
<td>14 CLINICAL STUDIES 14.2 Metastatic Gastrointestinal Cancer</td>
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**Metabolism and Genetic Polymorphism**

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%; approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient’s actual TPMT activity.

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

**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 homozygous 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: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%; approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient’s actual TPMT activity.

**Contraindications**

Evaluate patients with repeated severe myelosuppression for thrombotic CV events, for example, prior history of a CV event or stroke, in the BRILINTA arm did not depend on CYP2C19 loss of function status.

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|----------------------------------------|------|-----------------|-----------|-------------------|------------------|
| 207961, 02/22/2019                     | Tolterodine and Trifluridine (2) | Oncology | RAS        | Clinical Studies  | 14 CLINICAL STUDIES
|                                        |      |                 |           |                   | 14.1 Metastatic Colorectal Cancer
|                                        |      |                 |           |                   | (…) Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months) and region (Japan vs. US, Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS). A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab. (See Table 7)
| 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 (PMs) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. (…) 7 DRUG INTERACTIONS 7.1 Potent CYP2D6 Inhibitors
|                                        |      |                 |           |                   | Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine [see CLINICAL PHARMACOLOGY (12.1)]. The sum of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [see CLINICAL PHARMACOLOGY (12.3)]. 7.2 Potent CYP3A4 Inhibitors
|                                        |      |                 |           |                   | Ketoconazole (200 mg daily), a potent CYP3A4 inhibitor, increased the mean Cmax and AUC of tolterodine by 2- and 2.5-fold, respectively, in CYP2D6 poor metabolizers. For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, clarithromycin, or ritonavir, the recommended dose of DETROL LA is 2 mg once daily [see DOSAGE AND ADMINISTRATION(2.2) and CLINICAL PHARMACOLOGY (12.3)]. 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics
|                                        |      |                 |           |                   | 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 [approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs)] completed sequential 4-day periods of dosing with moxifloxacin 400 mg QD, tolterodine 2 mg BID, tolterodine 4 mg BID, and placebo. The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon coadministration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers [see DRUG INTERACTIONS (7.2)]. QT interval was measured over a 12-hour period following dosing, including the time of peak plasma concentration (Tmax) of tolterodine and at steady state (Day 4 of dosing). (…) 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” or “PMs”) is dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as “extensive metabolizers.” Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HMT. Excretion: Following administration of a 5 mg oral dose of 14C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (< 2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as 5-HMT.

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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>A summary of mean (± standard deviation) pharmacokinetic parameters of toremifene 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 toremifene extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM). (See Table 3)</td>
</tr>
<tr>
<td>020281, 04/08/2019</td>
<td>Tramadol</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Boxed Warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Patent Counseling Information</td>
<td>BOXED WARNING ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in all of the cases, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol (see WARNINGS).</td>
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<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
<td>BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma MEKINIST® is indicated, as a single agent 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), (2.2)]. BRAF V600E or V600K Mutation-Positive Metastatic Melanoma 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), (2.4)].</td>
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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 with 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 and dabrafenib [see Clinical Studies (14.1), (14.2)].
- Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics/NSCLC

- 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**

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.4)].

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

**Unresectable or Metastatic BRAF V600E Mutation Positive Melanoma**

MEKINIST Administered as a Single Agent

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

MEKINIST Administered with Dabrafenib

The safety of MEKINIST, administered with dabrafenib, was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma who received MEKINIST in two trials, the COMBI-d study (n = 209), a multicenter, double-blind, randomized (1:1), active-controlled trial and the COMBI-v study (n = 350), a multicenter, open-label, randomized (1:1), active-controlled trial. (...)

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

The safety of MEKINIST when administered with dabrafenib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study [see Clinical Studies (14.2)].

**Metastatic, BRAF V600E Mutation-Positive NSCLC**

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

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

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

### 12 CLINICAL PHARMACOLOGY

#### 12.2 Pharmacodynamics

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

#### 12.3 Pharmacokinetics

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

### 14 CLINICAL STUDIES

#### 14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

**Mekinist as a Single Agent**

The safety and efficacy of MEKINIST were evaluated in an international, multicenter, randomized (2:1), open-label, active-controlled trial (Trial 1) in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. (...)

Tumor tissue was evaluated for BRAF mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients (196 patients treated with MEKINIST and 93 chemotherapy-treated patients) were also tested retrospectively using an FDA-approved companion diagnostic test, THxID™-BRAF assay. (...)

The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (less than 1%). The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for patients treated with MEKINIST and 3.1 months for patients treated with chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST. (...)

**Mekinist with Dabrafenib**

The safety and efficacy of MEKINIST administered with dabrafenib were evaluated in an international, randomized, double-blind, active-controlled trial (the COMBI-d study; NCT01584648). The COMBI-d study compared dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive...
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<td>G6PD</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>MEKINIST administered with Dabrafenib (…) The trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVO or RPED, QTcB interval &gt;480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency.</td>
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<td>Trametinib (3)</td>
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<td>RAS</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 New Primary Malignancies</td>
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<td>Non-Cutaneous Malignancies</td>
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<td>Based on its mechanism of action, dabrafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms (refer to the Full Prescribing Information for dabrafenib). In the COMBI-d study, non-cutaneous malignancies occurred in 1.4% (3/209) of patients receiving MEKINIST plus dabrafenib and in 2.8% (6/211) of patients receiving single-agent dabrafenib. In Study BRF133928, non-cutaneous malignancies occurred in 1.1% (19/1819) of patients receiving MEKINIST with dabrafenib. Monitor patients receiving MEKINIST and dabrafenib closely for signs or symptoms of non-cutaneous malignancies. No dose modification is required for MEKINIST in patients who develop non-cutaneous malignancies [see Dosage and Administration (2.3)].</td>
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<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
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<th>Labeling Text‡</th>
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</table>
| 103792, 11/29/2018                     | Trastuzumab (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
   1.1 Adjuvant Breast Cancer
   Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer
   • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
   • with paclitaxel and carboplatin
   • as a single agent following multi-modality anthracycline based therapy.
   1.2 Metastatic Breast Cancer
   Herceptin is indicated:
   • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
   • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.
   1.3 Metastatic Gastric Cancer
   Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection
Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnosics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics
Cardiac Electrophysiology
The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer
The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

Studies 1 and 2
In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). (…)
Study 3
In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. (…)
(…) Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). (…)
Study 4
In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+) only as determined at a central laboratory. (…)
(…) Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available.

The results are shown in Table 10. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups. (See Table 10) (…)

14.2 Metastatic Breast Cancer
The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer in combination with chemotherapy and trastuzumab.

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breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab. Previously Untreated Metastatic Breast Cancer (Study 5) Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). (…) Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (See Table 12). (…) Previously Treated Metastatic Breast Cancer (Study 6) Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. (…) 14.3 Metastatic Gastric Cancer The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 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 (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%). (…) An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14. (See Table 14).

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<th>Oncology</th>
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<th>PRECAUTIONS Drugs Metabolized by CYP2D6</th>
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<td>Trastuzumab (2)</td>
<td>Oncology</td>
<td>Clinical Studies</td>
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<tr>
<td>12 CLINICAL STUDIES 14.1 Adjuvant Breast Cancer Study 4 (…) The final OS analysis results from Studies 1 and 2 indicate that OS benefit by 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 &gt; 50 years of age (n = 1868), 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 &gt; 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80). (See Table 9) (…)</td>
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| Tretinoin | Oncology                | PML-RARA                      |                                                      |                                        |
| 02/04/38, 07/01/2008 | Oncology               |                              |                                                      |                                        |

| Trimipramine | Psychiatry          | CYP2D6                          | Precautions                                         |                                        |
| 01/17/2014 |                        |                               |                                                      |                                        |

| Uremiclinium | Pulmonary            | CYP2D6                          | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics      |                                        |
| 20/03/19, 06/06/2019 | Pulmonary         |                               |                                                      |                                        |
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</table>
| 761044, 09/23/2016 | Ustekinumab | Dermatology and Gastroenterology | IL12A, IL12B, IL23A | Warnings and Precautions | **5 WARNINGS AND PRECAUTIONS**
5.2 Theoretical Risk for Vulnerability to Particular Infections
Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guérin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections.

Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances. |
| 209241, 08/10/2018 | Valsartan | Neurology | CYP2D6 | Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | **2 DOSAGE AND ADMINISTRATION**
2.3 Dosage Recommendations for Known CYP2D6 Poor Metabolizers
Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers (see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)). |
| 018081, 02/21/2019 | Valproic Acid (1) | Neurology | POLG | Boxed Warning, Contraindications, Warnings and Precautions | **BOXED WARNING**
WARNING: LIFE THREATENING ADVERSE REACTIONS
Patients with Mitochondrial Disease
There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g., Alpers-Huttenlocher Syndrome). Depakene is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder (see Contraindications (4)). In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice (see Warnings and Precautions (5.1)). |

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<td>018081, 02/21/2019</td>
<td>Valproic Acid (2)</td>
<td>Neurology</td>
<td>Nonspecific (Urea Cycle Disorders)</td>
<td>Contraindications, Warnings, Precautions</td>
<td>4 CONTRAINDICATIONS (…) Depakene is contraindicated in patients with known urea cycle disorders [see Warnings and Precautions (5.6)].</td>
</tr>
<tr>
<td>202429, 11/06/2017</td>
<td>Venurafenib (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 V600E 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 V600E mutations in melanoma is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 5 WARNINGS AND PRECAUTIONS 5.1 New Primary Malignancies (…) Other Malignancies Based on mechanism of action, ZELBORAF may promote malignancies associated with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies. 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>
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<td>Vemurafenib</td>
<td>Oncology</td>
<td>RAS</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>6 ADVERSE REACTIONS</td>
</tr>
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</table>

1. **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)].

2. **6.2 Pharmacodynamics**

   Cytidine Electrophysiology

   In a multi-center, open-label, single-arm study in 132 patients with BRAF V600E mutation-positive metastatic melanoma, patients administered vemurafenib 960 mg orally twice daily did not experience large changes in mean QTc interval (i.e., > 20 ms) from baseline.

3. **6.3 Pharmacokinetics**

   The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of 960 mg twice daily with dosing approximately 12 hours apart. The population pharmacokinetic analysis pooled data from 458 patients. At steady-state, vemurafenib exhibits linear pharmacokinetics within the 240 mg to 960 mg dose range.

4. **8.4 Pediatric Use**

   The safety and effectiveness of ZELBORAF in pediatric patients have not been established. Vemurafenib was studied in 6 adolescent patients 15 to 17 years of age with unresectable or metastatic melanoma with BRAF V600 mutation. A maximum tolerated dose was not reached with doses up to vemurafenib 960 mg twice daily. No new safety signals were observed. Vemurafenib steady-state exposure in these 6 adolescent patients was generally similar to that in adults.

5. **17 Patient Counseling Information**

   Healthcare providers should advise patients of the potential benefits and risks of ZELBORAF and instruct their patients to read the Medication Guide before starting ZELBORAF therapy. Inform patients of the following:

   - Evidence of BRAF V600E mutation in the tumor specimen with an FDA approved test is necessary to identify patients for whom treatment with ZELBORAF is indicated [see Dosage and Administration (2.1)].

6. **14 Clinical Studies**

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

   Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naive, BRAF V600E mutation-positive unresectable or metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, to receive ZELBORAF 960 mg by mouth twice daily (n=337) or dacarbazine 1000 mg/m² intravenously on Day 1 every 3 weeks (n=338). (See Table 5)(...) Patients with BRAF V600E Mutation-Positive Metastatic Melanoma Who Received Prior Systemic Therapy (ECD) In a single-arm, multicenter, multinational trial (Trial 2), 132 patients with BRAF V600E mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, who had received at least one prior systemic therapy, received ZELBORAF 960 mg by mouth twice daily. (...) Patients with BRAF V600E Mutation-Positive Melanoma with Brain Metastases The activity of ZELBORAF for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in an open-label, multicenter, single-arm, two cohort trial (Trial 3). (See Table 6)(...) Patients with Wild-Type BRAF Melanoma ZELBORAF has not been studied in patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].

7. **15 Non-Malignant Side Effects**

   The following side effects were reported during post approval use of ZELBORAF.

   - Nephropathy benign, malignant and unspecified (incl. cysts and polyps)

8. **16.2 Postmarketing Experience**

   The following adverse reactions have been identified during post approval use of ZELBORAF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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9. **5.2 WARNINGS AND PRECAUTIONS**

   Other Malignancies

   Based on mechanism of action, ZELBORAF may promote malignancies associated with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies.
### Table of Pharmacogenomic Biomarkers in Drug Labeling

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| 020699, 12/19/2017                   | Venetoclax | Psychiatry | CYP2D6 | Drug Interactions, Use in Specific Populations, Clinical Pharmacology | 7 DRUG INTERACTIONS  
7.5 Weight Loss Agents  
The safety and efficacy of venetoclax therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. (See Figure 1) |
| 208573, 05/15/2019                   | Venetoclax (1) | Oncology | Chromosome 17p | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy  
MURANO  
(….) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/ cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (See Table 21) (….)  
Monotherapy  
The efficacy of VENCLEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies.  
Study M13-982  
The efficacy of VENCLEXTA was established in study M13-982 (NCT01889186), an open-label, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. (See Table 23) (….)  
Study M12-175  
Study M12-175 (NCT01328628) 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 VENCLEXTA. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months). The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)  
Study M14-032  
Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≥5 cm, 31% had an absolute lymphocyte count ≥35 x 10⁹ /L, 57% had documented unmutated IgVH, and 38% had documented 17p deletion. (…) |
| 208573, 05/15/2019                   | Venetoclax (2) | Oncology | Chromosome 11q | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy  
CELLS  
(….) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…)  
MURANO  
(….) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…) |
| 208573, 05/15/2019                   | Venetoclax (3) | Oncology | TP53 | Clinical Studies | 14 CLINICAL STUDIES  
14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy  
CELLS  
(….) 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%. (…) |

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<td>IDH1</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 aged 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)</td>
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<td>IDH2</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 aged 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)</td>
</tr>
<tr>
<td>Venetoclax (6)</td>
<td>Oncology</td>
<td>IGH</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Combination Therapy COIL6 (…) The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had ClCr&lt;70 mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmutated IgVH in 57%. (…) MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (See Table 17) (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)</td>
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<td>Venetoclax (7)</td>
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<td>NPM1</td>
<td>Clinical Studies</td>
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</thead>
</table>
| 204447, 10/19/2018 | Vortioxetine | Psychiatry | CYP2D6 | Dosage and Administration, Clinical Pharmacology | 2 DOSE 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., sibutramine, 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)]. |
| 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 than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts. (…) |
| 200497, 08/09/2012 | Vincristine | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Adult ALL in Second or Greater Relapse
Marqibo® is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified. |
| 208573, 05/15/2019 | Venetoclax (8) | Oncology | FLT3 | Clinical Studies | 14 CLINICAL STUDIES
14.2 Acute Myeloid Leukemia
Study M14-352
Venetoclax was studied in a non-randomized, open-label clinical trial (NCT0203773) of VENCLEXTA in combination with azacitidin (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 70 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) (…) |

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Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2019

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<th>Labeling Sections</th>
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</tr>
</thead>
</table>
| 009218, 08/14/2017                     | Warfarin (1)          | Hematology       | CYP2C9     | Dosage and Administration, Drug Interactions, Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism and Elimination
Warfarin is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronide acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vitamin K to its major pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vitamin K plasma concentration of extensive metabolizers. (…)

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
If the patient’s CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg once daily. Determine each patient’s dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily.
Dosing Recommendations with Consideration of Genotype
Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see Clinical Pharmacology (12.5)]. If the patient’s CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>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
12.3 Pharmacokinetics
Metabolism
The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic cytochrome P-450 (CYP450) microsomal enzymes to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols) with minimal anticoagulant activity. Identified metabolites of warfarin include dehydrowarfarin, two diastereomeric alcohols, and 4′, 6′, 7′, 8′, and 10′-hydroxycoumarin. CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, CYP1A2, CYP2C19, and CYP2C8. Inhibition or induction of these CYP450 isozymes can alter warfarin metabolism and affect its anticoagulant activity. Certain CYP2C9 alleles are associated with reduced warfarin metabolism and increased risk of adverse bleeding events. Patients with one or more CYP2C9 allele(s) have decreased warfarin clearance and increased risk of adverse bleeding. (…)

Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose of warfarin [see Dosage and Administration (2.3)].

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| 009218, 08/14/2017                     | Warfarin (2)          | Hematology       | VKORC1     | Dosage and Administration, Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism
The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic cytochrome P-450 (CYP450) microsomal enzymes to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols) with minimal anticoagulant activity. Identified metabolites of warfarin include dehydrowarfarin, two diastereomeric alcohols, and 4′, 6′, 7′, 8′, and 10′-hydroxycoumarin. CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, CYP1A2, CYP2C19, and CYP2C8. Inhibition or induction of these CYP450 isozymes can alter warfarin metabolism and affect its anticoagulant activity. Certain CYP2C9 alleles are associated with reduced warfarin metabolism and increased risk of adverse bleeding events. Patients with one or more CYP2C9 allele(s) have decreased warfarin clearance and increased risk of adverse bleeding. (…)

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
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If the patient’s CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg once daily. Determine each patient’s dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily.
Dosing Recommendations with Consideration of Genotype
Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see Clinical Pharmacology (12.5)]. If the patient’s CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>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
12.3 Pharmacokinetics
Metabolism
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<td>009218, 08/14/2017</td>
<td>Warfarin (3)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
<td>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>009218, 08/14/2017</td>
<td>Warfarin (4)</td>
<td>Hematology</td>
<td>PROC</td>
<td>Warnings and Precautions</td>
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