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

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

<table>
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<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</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)]. (...)
| 208716, 06/17/2018                     | Abemaciclib (1) | Oncology | ESR | Indications and Usage, Adverse | 1 INDICATIONS AND USAGE VERZENOVO™ (abemaciclib) is indicated: |

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<td>(Hormone Receptor)</td>
<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.</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.</td>
</tr>
</tbody>
</table>

6 ADVERSE REACTIONS

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

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

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

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

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

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

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotheraphy 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 (NCT0107703) was a randomized, double-blind, 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. (…) MONARCH 1 was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. (…)

1 INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotheraphy 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. (…) MONARCH 1 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. (…)

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<td>125427, 07/25/2016</td>
<td>Ado-Trastuzumab Emtansine</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>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. (…)</td>
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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-blind, 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. (…) |

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The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial 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. (…)

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

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC
2.1.1 Patient Selection for Non-Resistant EGFR Mutation-Positive Metastatic NSCLC
Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of non-resistant EGFR mutations in tumor specimens [see Indications and Usage (1.1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnoses.

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

The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 3). (…)

14 CLINICAL STUDIES
14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer
The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall survival (OS), EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial (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 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 [NCT0121393]). • LUX-Lung 2 was a single arm, multicenter study of afatinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue.

• LUX-Lung 3 was a randomized, multicenter study comparing treatment with afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RQG PCR kit.

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

Among the 75 GILOTRIF treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. Among the 32 patients with a confirmed non-resistant EGFR mutation, the median age was 60.5 years (range 32-79), 66% were female, 97% were Asian, 3% were other races, 38% had an ECOG PS of 0, 63% had an ECOG PS 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIIb disease, and 88% had received no prior systemic therapy for advanced or metastatic disease.

The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.
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<td>Pharmacology, Clinical Studies</td>
<td><strong>Select patients for the treatment of metastatic NSCLC with ALECENSA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</strong></td>
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</table>

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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

**Previously Untreated ALK-Positive Metastatic NSCLC**

The safety of ALECENSA was evaluated in 152 patients with ALK-positive NSCLC in the ALEX study. The median duration of exposure to ALECENSA was 17.9 months. (**...**) ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib

The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with ALECENSA in two clinical trials, Studies NP28761 and NP28673. (**...**)  

#### 12 CLINICAL PHARMACOLOGY

##### 12.3 Pharmacokinetics

The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects. In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation (%)) steady-state maximal concentration (Cmax,ss) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. (**...**) Absorption

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 FDAapproved test, and ECOG PS of 0-2 were enrolled in both studies. (**...**)  

### 8 USE IN SPECIFIC POPULATIONS

#### 8.8 NAT2 Poor Metabolizers

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

#### 12 CLINICAL PHARMACOLOGY

##### 12.2 Pharmacodynamics

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

##### 12.5 Pharmacogenomics

Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of FIRDAPSE metabolism. Poor metabolizers, also referred to as “slow acetators” (i.e., carriers of two reduced function alleles), have 3.5- to 4.5-fold higher Cmax, and 5.6- to 9-fold higher AUC than normal metabolizers, also referred to as “fast acetators.”

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<td>Amtriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Drugs Metabolized by P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called &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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<td>Psychiatry</td>
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<td>PRECAUTIONS Drug Interactions Drugs Metabolized by P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called &quot;poor metabolizers&quot;); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. (…)</td>
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<td>204325, 09/15/2017</td>
<td>Anastrozole</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Adjuvant Treatment ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. 1.2 First-Line Treatment ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer. 1.3 Second-Line Treatment ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience A post-marketing trial assessed the combined effects of ARIMIDEX and the bisphosphonate risendronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture. (…) 7 DRUG INTERACTIONS 7.1 Tamoxifen Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial [see Clinical Studies (14.1)]. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole. (…) 14 CLINICAL STUDIES 14.1 Adjuvant Treatment of Breast Cancer in Postmenopausal Women</td>
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<tr>
<td>021912, 02/27/2014</td>
<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. (…) Patients in the two monotherapy arms of the ATAC trial were treated for a median of 60 months (5 years) and followed for a median of 68 months. Disease-free survival in the intent-to-treat population was statistically significantly improved [Hazard Ratio (HR) = 0.87, 95% CI: 0.78, 0.97, p=0.0127] in the ARIMIDEX arm compared to the tamoxifen arm. In the hormone receptor-positive subpopulation representing about 84% of the trial patients, disease-free survival was also statistically significantly improved (HR = 0.83, 95% CI: 0.73, 0.94, p=0.0049) in the ARIMIDEX arm compared to the tamoxifen arm. (See Figure 2) (…) The frequency of individual events in the intent-to-treat population and the hormone receptor-positive subpopulation are described in Table 8. (see Table 8) A summary of the study efficacy results is provided in Table 9. (See Table 9, 10, and Figure 4) (…)</td>
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<tr>
<td>021912, 02/27/2014</td>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Demethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities</td>
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<tr>
<td>021436, 08/18/2016</td>
<td>Aripiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.7 Dosage Adjustments for Cytochrome P450 Considerations Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered drug is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response. (See Table 2)</td>
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<td>207533, 08/18/2016</td>
<td>Lauroxil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>2.4 Dose Adjustments for CYP450 Considerations*</td>
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<td>021248, 02/20/2015</td>
<td>Arsenic Trioxide</td>
<td>Oncology</td>
<td>PML-RARA</td>
<td>Indications and Usage</td>
<td>Refer to the prescribing information for oral aripiprazole for recommendations regarding dosage adjustments due to drug interactions, for the first 21 days when the patient is taking oral aripiprazole concomitantly with the first dose of ARISTADA. Once stabilized on ARISTADA, refer to the dosing recommendations below for patients taking CYP 2D6 inhibitors, CYP 3A4 inhibitors, or CYP 3A4 inducers: • No dosage changes recommended for ARISTADA if CYP 450 modulators are added for less than 2 weeks. • Make dose changes to ARISTADA if CYP 450 modulators are added for greater than 2 weeks. (See Table 4)</td>
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<tr>
<td>022406, 11/02/2018</td>
<td>Articaine and Epinephrine (1)</td>
<td>Anesthesiology</td>
<td>GPiPD</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 idiosyncratic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<tr>
<td>022406, 11/02/2018</td>
<td>Articaine and Epinephrine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiosyncratic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<tr>
<td>761034, 12/08/2018</td>
<td>Atezolizumab (1)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage</td>
<td>1 INDICATIONS AND USAGE 1.1 Locally Advanced or Metastatic 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), or • are not eligible for any platinum-containing chemotherapy regardless of level of tumor PD-L1 expression, or • have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. 2 DOSAGE AND ADMINISTRATION 2.1 Selection of Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Carcinoma 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)]. Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a> 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Previously Treated Metastatic NSCLC</td>
</tr>
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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>12.3 Pharmacokinetics</td>
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<td>Specific Populations</td>
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<td>Age (21–89 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m²), mild hepatic impairment (bilirubin ≤ ULN and AST &gt; ULN or bilirubin &gt; 1.0 to 1.5 × ULN and any AST), level of PD-L1 expression, or EOCG status had no clinically significant effect on the systemic exposure of atezolizumab. (…)</td>
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<td>14.1 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). Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an EOCG PS of 0 or 1. Reasons for inelegibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an EOCG PS of 2, 16% had a hearing loss ≥ 25 dB, and 9% had Grade 2-4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 10. 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 8)</td>
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<td>(…) IMvigor130 (NCT02807636) is an ongoing multicenter, randomized study in formerly untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study contains three arms: TECENTRIQ monotherapy, TECENTRIQ with platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine), and platinum-based chemotherapy alone ( comparator). 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 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>(…) Previously Treated 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 310 patients, 32% 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 68% of patients were classified as having PD-L1 expression of &lt; 5% of the tumor area). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 11. The median follow-up time for this cohort was 14.4 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%). (see Table 11) (…)</td>
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<td>14.2 Metastatic Non-Small Cell Lung Cancer</td>
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<td>Metastatic Chemotherapy-Naive Non-Squamous NSCLC</td>
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<td>The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with 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 EOCG performance status 0 or 1. (…) Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following three treatment arms. (…) 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. (See Table 12) (…)</td>
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<td>(…) Previously Treated Metastatic NSCLC</td>
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<td>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. (See Table 13) (…)</td>
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| 761034, 12/06/2018 | Atezolizumab (2) | Oncology | Gene Signature (T-effector) | Clinical Studies | 14 CLINICAL STUDIES  
14.2 Metastatic Non-Small Cell Lung Cancer  
Metastatic Chemotherapy-Naive Non-Squamous NSCLC  
The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (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 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 effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITTW蒂 population and overall survival (OS) in the ITTW蒂 population.  
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 ITTW蒂 subpopulations.  
A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT蒂 subpopulation and 447 were in the IGE-WT蒂 subpopulation. (…)  
(The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the IGE-WT蒂 subpopulation, 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蒂 subpopulation are presented in Table 12 and Figure 1. (…)  

5.12 Laboratory Tests  
Routine laboratory tests are not required. CYP2D6 metabolism- Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA [see Adverse Reactions (6.1)].  
5.13 Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients who are known to be CYP2D6 PMs  
Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. Dosage adjustment of STRATTERA may be necessary when coadministered with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine) or when administered to CYP2D6 PMs. [See Dosage and Administration (2.4) and Drug Interactions (7.2)].  

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Child and Adolescent Clinical Trials  
(…) The following adverse reactions occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: insomnia (11% of PMs, 6% of EMs; weight decreased (7% of PMs, 4% of EMs; constipation (7% of PMs, 4% of EMs; depression (7% of PMs, 4% of EMs; tremor (5% of PMs, 1% of EMs; excitation (4% of PMs, 2% of EMs; middle insomnia (3% of PMs, 1% of EMs; conjunctivitis (3% of PMs, 1% of EMs; early morning awakening (2% of PMs, 1% of EMs; mydriasis (2% of PMs, 1% of EMs; sedation (4% of PMs, 2% of EMs; (…)  

Adult Clinical Trials  
(…) The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metaboliser (EM) patients: vision blurred (4% of PMs, 1% of EMs; dry mouth (3% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs; feeling jittery (5% of PMs, 2% of EMs; decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs; insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs; middle insomnia (3% of PMs, 3% of EMs; terminal insomnia (3% of PMs, 1% of EMs; urinary retention (6% of PMs, 2% of EMs; (…)  

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<td>PMs, 1% of EMs; erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (6% of PMs, 2% of EMs); hyperhidrosis (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of EMs). (…)</td>
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### 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)].

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

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

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

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

Absorption and distribution
Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (Cmax) are reached approximately 1 to 2 hours after dosing. (…) Metabolism and elimination
Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and Cmax is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary [see Warnings and Precautions (5.13)].

Atomoxetine did not inhibit or induce the CYP2D6 pathway.
The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated.
4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 2.16 hours. For PMs, AUC of atomoxetine is approximately 10-fold and Cmax is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours). (…)
<table>
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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<tr>
<td>021881, 12/17/2013</td>
<td>Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate</td>
<td>Gastroenterology</td>
<td>GPDP</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.8 Glucose-6-phosphate dehydrogenase (G-6-PD) Deficiency Since Moviprep contains sodium ascorbate and ascorbic acid, Moviprep should be used with caution in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, especially G-6-PD deficiency patients with an active infection, with a history of hemolysis, or taking concomitant medications known to precipitate hemolytic reactions.</td>
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<tr>
<td>210238, 05/21/2018</td>
<td>Avatrombopag (1)</td>
<td>Hematology</td>
<td>F2 (Prothrombin)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and 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, 05/21/2018</td>
<td>Avatrombopag (2)</td>
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<td>F5 (Factor V Leiden)</td>
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</tr>
<tr>
<td>210238, 05/21/2018</td>
<td>Avatrombopag (3)</td>
<td>Hematology</td>
<td>PROC</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and 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, 05/21/2018</td>
<td>Avatrombopag (4)</td>
<td>Hematology</td>
<td>PROS1</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and 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>
</tr>
<tr>
<td>210238, 05/21/2018</td>
<td>Avatrombopag (5)</td>
<td>Hematology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.</td>
</tr>
<tr>
<td>761049, 03/23/2017</td>
<td>Avelumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (...) A total of 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression: of these, 66% were PD-L1-positive (≥ 1% of tumor cells), 16% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCPyV) using an investigative assay, of the 77 patients with evaluable results, 52% had evidence of MCPyV.</td>
</tr>
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<tr>
<td>016324, 12/20/2018</td>
<td>Azathioprine (1)</td>
<td>Rheumatology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings, Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology</td>
<td>Efficacy results are presented in Table 4. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV. (See Table 4)</td>
</tr>
</tbody>
</table>

**DOSAGE AND ADMINISTRATION**

Patients with TPMT and/or NUDT15 Deficiency

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

Homozygous deficiency in either TPMT or NUDT15

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

Heterozygous deficiency in TPMT and/or NUDT15

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

**WARNINGS**

Cytopenias

TPMT or NUDT15 Deficiency

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

**PRECAUTIONS**

TPMT and NUDT15 Testing: Consider genotyping or phenotyping patients for TPMT deficiency and genotyping for NUDT1 deficiency in patients with severe myelosuppression. TPMT and NUDT15 testing cannot substitute for complete blood count (CBC) monitoring in patients receiving IMURAN. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections). Drug Interactions Use with Allopurinol: One of the pathways for inactivation of azathioprine is inhibited by allopurinol. Patients receiving IMURAN and allopurinol concomitantly should have a dose reduction of IMURAN, to approximately 1/2 to 1/4 the usual dose. It is recommended that a further dose reduction or alternative therapies be considered for patients with low or absent TPMT activity receiving IMURAN and allopurinol because both TPMT and XO inactivation pathways are affected. See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS: Laboratory Tests and ADVERSE REACTIONS sections.

**ADVERSE REACTIONS**

Hematologic

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

**CLINICAL PHARMACOLOGY**

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

Genetic polymorphisms influence TPMT and NUDT15 activity. Several published studies indicate that patients with reduced TPMT and 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. (…)

| 016324, 12/20/2018 | Azathioprine (2) | Rheumatology | NUDT15 | Dosage and Administration, Warnings, Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology | DOSAGE AND ADMINISTRATION

Patients with TPMT and/or NUDT15 Deficiency

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

Homozygous deficiency in either TPMT or NUDT15

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

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<tbody>
<tr>
<td>206256, 07/03/2014</td>
<td>Belinostat</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>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).</td>
</tr>
<tr>
<td>210498, 06/27/2018</td>
<td>Binimetinib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in</td>
<td>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).</td>
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<td>Clinical Pharmacology</td>
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<tr>
<td>125557, 08/30/2016</td>
<td>Blinatumomab</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Clinical Studies</td>
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<td>202258, 01/30/2017</td>
<td>Boceprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology</td>
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</table>

**5 WARNINGS AND PRECAUTIONS**

**5.3 Ocular Toxicities**

Retinal Vein Occlusion

RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 1 patient experienced RVO (0.1%).

**5.4 Interstitial Lung Disease**

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

**5.5 Rhabdomyolysis**

Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevated levels of serum CPK occurred in 58% of patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), rhabdomyolysis was reported in 0.1%.

**6 ADVERSE REACTIONS**

The data described below reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in a randomized open-label, active-controlled trial (COLUMBUS) or, for rare events, exposure of 690 patients with BRAF V600 mutation- positive melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials. The data described below reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in COLUMBUS.

**8 USE IN SPECIFIC POPULATIONS**

**8.5 Geriatric Use**

Of the 690 patients with BRAF mutation-positive melanoma who received MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of MEKTOVI plus encorafenib were observed in elderly patients compared to younger patients (see Clinical Pharmacology (12.3)).

**14 CLINICAL STUDIES**

MEKTOVI in combination with encorafenib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS: NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Based on central testing, 100% of patients’ tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%).

**12 CLINICAL PHARMACOLOGY**

**12.3 Pharmacokinetics**

Drug interaction studies (see Dosage and Administration (2.1)).

**12.4 Lactation**

It is not known whether binimetinib is excreted in breast milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**12.5 Pharmacokinetics**

A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to PegIntron/REBETOL. IL28B rs12979860 was genotyped in 653 of 1048 (62%) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPOND-2 (previous partial responders and relapsers) [see Clinical Studies (14) for trial descriptions]. Among subjects that received at least one dose of placebo or VICTRELIS (Modified-Intent-to-Treat population), SVR rates tended to be lower in subjects with the C/T and T/T genotypes compared to those with the C/C genotype, particularly among previously untreated subjects receiving 48 weeks of PegIntron and REBETOL (see Table 9). Among previous treatment failures, subjects of all genotypes appeared to have similar responses.

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<td>Bosutinib</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>BOSULIF is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.</td>
</tr>
<tr>
<td>125388, 11/16/2018</td>
<td>Brentuximab</td>
<td>Oncology</td>
<td>ALK</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>14.2 Systemic Anaplastic Large Cell Lymphoma Clinical Trial in Relapsed sALCL (Study 2)</td>
<td>(…) 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>1.6 Relapsed primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF)</td>
<td>ADCETRIS is indicated for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>2 DOSAGE AND ADMINISTRATION</td>
<td>2.1 Recommended Dosage</td>
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<td></td>
<td></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>
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ADСETRIS 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 ADСETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician’s choice of either methotrexate 5 to 10 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 ADСETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHELON-2), 31% of ADСETRIS + CHP-treated patients were age 65 or older. (…) In the clinical trial of ADСETRIS in pcALCL or CD30-expressing MF (Study 4: ALCANZA), 42% of ADСETRIS-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 ADСETRIS 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 ADСETRIS in patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) requiring systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. (…) Patients with pcALCL must have received prior radiation or systemic therapy, and must have at least 1 biopsy with CD30-expression of ≥10%. Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30-expression of ≥10% in at least 1 biopsy. A total of 131 patients were randomized (66 ADСETRIS, 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 ADСETRIS 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.
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<tr>
<td>205838, 06/03/2016</td>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. (...)</td>
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<tr>
<td>009366, 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>203758, 05/20/2016</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 92% had undergone a thyroidectomy. The RET mutation status determined by a research use assay was positive in 51%, negative in 14%, and was unknown in 35%. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI. (...)</td>
</tr>
<tr>
<td>020896, 12/14/2016</td>
<td>Capecitabine</td>
<td>Oncology</td>
<td>DPD</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. Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No XELODA dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.</td>
</tr>
<tr>
<td>016608, 08/28/2015</td>
<td>Carbamazepine (1)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>BOXED WARNING Serious dermatologic reactions and HLA-B<em>1502 allele Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B</em>1502, an inherited allelic variant of the HLA-B gene. HLA-B<em>1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B</em>1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk (see WARNINGS AND PRECAUTIONS, Laboratory Tests). (...)</td>
</tr>
<tr>
<td>016608</td>
<td>Carbamazepine (2)</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. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Tegretol should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. SJS/TEN and HLA-B</em>1502 Allele Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B<em>1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity. Across Asian populations, notable variation exists in the prevalence of HLA-B</em>1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B<em>1502, averaging 2% to 4%, but higher in some groups. HLA-B</em>1502 is present in less than 1% of the population in Japan and Korea. HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).</td>
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<td>016608, 08/28/2015</td>
<td>Carbamazepine (2)</td>
<td>Neurology</td>
<td>HLA-A</td>
<td>Warnings</td>
<td>Prior to initiating Tegretol therapy, testing for HLA-B<em>1502 should be performed in patients with ancestry in populations in which HLA-B</em>1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B<em>1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Tegretol should not be used in patients positive for HLA-B</em>1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see BOXED WARNING and PRECAUTIONS, Laboratory Tests). Over 90% of Tegretol treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Tegretol. The HLA-B<em>1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from Tegretol such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Limited evidence suggests that HLA-B</em>1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.</td>
</tr>
<tr>
<td>022562, 08/05/2013</td>
<td>Carglumic Acid</td>
<td>Inborn Errors of Metabolism</td>
<td>NAGS</td>
<td>Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>WARNINGS</td>
</tr>
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<td>Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A<em>3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJ/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (see DRESS/Multiorgan hypersensitivity below). HLA-A</em>3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (for example, Tamil Nadu) and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American, and other Indian ancestry; and up to about 5% in African-Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry. The risks and benefits of Tegretol therapy should be weighed before considering Tegretol in patients known to be positive for HLA-A<em>3101. Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B</em>1502-positive and HLA-A<em>3101-positive patients treated with Tegretol will not develop SJ/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B</em>1502-negative and HLA-A*3101-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJ/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring, have not been studied.</td>
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<td>204370, 11/06/2017</td>
<td>Cariprazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>The efficacy of Cariprazine for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began Cariprazine treatment during infancy or childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Cariprazine, however, data are limited.</td>
</tr>
<tr>
<td>011792, 02/01/2013</td>
<td>Carisoprodol</td>
<td>Rheumatology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>The use of Carisoprodol in patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients [see Clinical Pharmacology (12.3)].</td>
</tr>
<tr>
<td>020297, 10/02/2015</td>
<td>Carvedilol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+)-enantiomer of carvedilol [see Clinical Pharmacology (12.3)]. Retrospective analysis of side effects in clinical trials showed that poor metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.</td>
</tr>
<tr>
<td>020998, 05/09/2016</td>
<td>Celecoxib</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)].</td>
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<td>8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see Poor Metabolizers of CYP2C9 substrates (8.8)]. 8.8 Poor Metabolizers of CYP2C9 Substrates In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9<em>3/<em>3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer CELEBREX starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)]. 12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9</em>2 and CYP2C9</em>3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/<em>3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9</em>1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosing (2.6), Use in Specific Populations (8.8)].</td>
</tr>
<tr>
<td>050585, 07/12/2018</td>
<td>Ceftriaxone (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings</td>
<td>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. (…)</td>
</tr>
<tr>
<td>050585, 07/12/2018</td>
<td>Ceftriaxone (2)</td>
<td>Infectious Diseases</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>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. (…)</td>
</tr>
<tr>
<td>205755, 05/26/2017</td>
<td>Ceritinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>1 INDICATIONS AND USAGE ZYKADIA® is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a> 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 625 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. (…) Previously Untreated ALK-Positive Metastatic NSCLC The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study (ASCEND-4, NCT01828099). 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, NCT01528099). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. (…)</td>
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<td>Cerliponase Alfa</td>
<td>Inborn Errors of Metabolism</td>
<td>TPP1</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Studies</td>
<td>The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (ASCEND-1, NCT01283516). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily. (…) ALK-positivity was verified retrospectively by review of local test results for 99% of patients. (…)</td>
</tr>
<tr>
<td>125084, 10/11/2016</td>
<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: Binireuka is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. 8 USE IN SPECIFIC POPULATIONS: 8.4 Pediatric Use: Safety and effectiveness of Binireuka have been established in pediatric patients 3 years of age and older. Pediatric use of Binireuka to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established. 14 CLINICAL STUDIES: The efficacy of Binireuka was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established. 14 CLINICAL STUDIES: The efficacy of Binireuka was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established. 14 CLINICAL STUDIES: The efficacy of Binireuka was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established. 14 CLINICAL STUDIES: The efficacy of Binireuka was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established.</td>
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<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td>(…) Table 4 contains selected adverse reactions in 667 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer receiving EU-approved cetuximab plus FOLFIRI or FOLFIRI alone in Study 4 (see Warnings and Precautions (5.8)). (See Table 4) (…) Erbitux Monotherapy (…) Table 5 contains selected adverse reactions in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer who received best supportive care (BSC) alone or with Erbitux in Study 5 (see Warnings and Precautions (5.8)). Erbitux was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range 1–51). (See Table 5) (…)</td>
</tr>
</tbody>
</table>

14 CLINICAL STUDIES
14.2 Colorectal Cancer
Erbitux Clinical Trials in K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer
Study 4 was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, metastatic colorectal cancer. (See Table 8) (…) Study 5 was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent mCRC. (See Table 9) (…) Study 6 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. (…)

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Colorectal Cancer
Study 4: EU-Approved Cetuximab in Combination with FOLFIRI (…) Table 4 contains selected adverse reactions in 667 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer receiving EU-approved cetuximab plus FOLFIRI or FOLFIRI alone in Study 4 (see Warnings and Precautions (5.8)). Cetuximab was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 26 infusions (range 1–224). (See Table 4) (…) Erbitux Monotherapy (…) Table 5 contains selected adverse reactions in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer who received best supportive care (BSC) alone or with Erbitux in Study 5 (see Warnings and Precautions (5.8)). Erbitux was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range 1–51). (See Table 5) (…) |

14 CLINICAL STUDIES
14.2 Colorectal Cancer
Erbitux Clinical Trials in K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer
(…) K-Ras mutation status was available for 1079/1217 (89%) of the patients: 676 (63%) patients had K-Ras wild-type tumors and 403 (37%) patients 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 Warnings and Precautions (5.7)]. Base characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population (see Warnings and Precautions (5.7)). (…) |

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<td></td>
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<tr>
<td>020989, 12/08/2006</td>
<td>Cevimeline</td>
<td>Dental</td>
<td>CYP2D6</td>
<td>Precautions</td>
<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>
</tr>
<tr>
<td>006002, 11/06/2013</td>
<td>Chloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Hematological Effects/Laboratory Tests Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered. The drug should be administered with caution to patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency. (…)</td>
</tr>
<tr>
<td>01641, 02/01/2011</td>
<td>Chloropropamide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS Hemolytic Anemia Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonamide agents can lead to hemolytic anemia. Because DIABINESSE belongs to the class of sulfonamide agents, caution should be used in patients with G6PD deficiency and a non-sulfonamide alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. (…)</td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chlorprocaincine (1)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>009435, 11/02/2018</td>
<td>Chlorprocaincine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
</tr>
<tr>
<td>018057, 02/26/2015</td>
<td>Cisplatin</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Adverse Reactions</td>
<td>6 ADVERSE REACTIONS Ototoxicity. (…) Genetic factors (e.g., variants in the thiorpurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.</td>
</tr>
<tr>
<td>020822, 01/04/2017</td>
<td>Citalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Warnings, Clinical Pharmacology</td>
<td>DOSAGE AND ADMINISTRATION Special Populations 20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age, patients with hepatic impairment, and for CYP2C19 poor metabolizers or those patients taking cimetidine or another CYP2C19 inhibitor. (see WARNINGS) WARNINGS QT-Prolongation and Torsade de Pointes The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected. CLINICAL PHARMACOLOGY Pharmacokinetics Population Subgroups (…) CYP2C19 poor metabolizers – In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Clexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION). CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.</td>
</tr>
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<tr>
<td>020822, 01/04/2017</td>
<td>Citalopram (2)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY Pharmacokinetics Population Subgroups CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6. Drug-Drug Interactions Co-administration of a drug that inhibits CYP2D6 with Citalopram is unlikely to have clinically significant effects on citalopram metabolism, based on the study results in CYP2D6 poor metabolizers.</td>
</tr>
<tr>
<td>202067, 06/10/2018</td>
<td>Clozapam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers In CYP2C19 poor metabolizers, levels of N-desmethylclozapam, clozapam’s active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 [see Use in Specific Populations (8.6), Clinical Pharmacology (12.5)].</td>
</tr>
<tr>
<td>019906, 07/28/2014</td>
<td>Clomipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Drugs Metabolized by P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA) (…).</td>
</tr>
<tr>
<td>020839, 09/16/2016</td>
<td>Clopidogrel</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>BOXED WARNING WARNING Diminished antiplatelet effect in patients with two-loss-of-function alleles of the CYP2C19 gene The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed “CYP2C19 poor metabolizers”). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.</td>
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</tr>
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<tr>
<td>019758, 02/23/2017</td>
<td>Clozapine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. (See Table 3)</td>
</tr>
<tr>
<td>206192, 05/31/2016</td>
<td>Cobimetinib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: 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>
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<tr>
<td></td>
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<td></td>
<td>2 DOSAGE AND ADMINISTRATION: 2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers</td>
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<td>It may be necessary to reduce the CLOZARIL dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)].</td>
</tr>
<tr>
<td>022402, 12/16/2016</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>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)]. (…)</td>
</tr>
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<td>14 CLINICAL STUDIES: The safety and efficacy of cobimetinib was established in a multicenter, randomized (1:1), double-blind, placebo-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation test. (…) (…) The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review. A trend favoring the cobimetinib with vemurafenib arm was observed in exploratory subgroup analyses of PFS, OS, and ORR in both BRAF V600 mutation subtypes (V600E or V600K) in the 81% of patients in this trial where BRAF V600 mutation type was determined.</td>
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<td>202570, 01/24/2017</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>dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)]. Children with obstructive sleep apnea who are treated with codeine for post tonsillectomy and/or adenoidectomy may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine.</td>
</tr>
</tbody>
</table>

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

8.4 Pediatric Use
The safety and effectiveness and the pharmacokinetics of Codeine Sulfate Tablets in pediatric patients below the age of 18 have not been established. Respiratory depression and death have occurred in children with obstructive sleep apnea who received Codeine Sulfate Tablets in the post-operative period following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)].

17 PATIENT COUNSELING INFORMATION
Ultra-Rapid Codeine Metabolizers
Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are ultra-rapid codeine metabolizers or not. These higher-than-normal levels of morphine in the blood may lead to life threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing [see Warnings and Precautions (5.4)]. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Codeine is contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine for other reasons to monitor for signs of respiratory depression.

1 INICATIONS AND USAGE
1.1 ALK-Positive Metastatic NSCLC
XALKORI 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 [see Clinical Studies (14.1)].

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Indications and Usage (1.1, 1.2) and Clinical Studies (14.1, 14.2)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/inVitroDiagnostics/ucm301431.htm. An FDA-approved test for the detection of ROS1 rearrangements in NSCLC is not currently available. Refer to Section 14.2 for information on the tests used in the clinical study to identify patients with ROS1 rearrangements in NSCLC.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…) The data in the Warnings and Precautions section reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm), 2, 3, a single arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154) [see Warnings and Precautions (5)]. The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3) (…) Previously Untreated ALK-Positive Metastatic NSCLC - Study 1
The data in Table 3 are derived from 340 patients with ALK-positive metastatic NSCLC who had not received previous systemic treatment for advanced disease who received treatment in a randomized, multicenter, open-label, active-controlled trial (Study 1) (…) Previously Treated ALK-Positive Metastatic NSCLC - Study 2 The data in the Table 3 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 2) (…) Renal impairment

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<td>Crizotinib (2)</td>
<td>Oncology</td>
<td>ROS1</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>(…) The estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m² (n=1681) to a median of 80.23 mL/min/1.73 m² at 2 weeks (n=1499) in patients with ALK-positive advanced NSCLC who received XALKORI in clinical trials. (…)</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac electrophysiology

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

14 CLINICAL STUDIES

14.1 ALK-Positive Metastatic NSCLC

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1

The efficacy and safety of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active controlled study (Study 1). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit, prior to randomization. (See Table 7) (…) Previously Treated ALK-Positive Metastatic NSCLC - Study 2

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

14.2 ROS1-Positive Metastatic NSCLC

Previously Untreated ROS1-Positive Metastatic NSCLC - Study 3

The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI (Study 3) (…) XALKORI is indicated for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Indications and Usage (1.1, 1.2) and Clinical Studies (14.1, 14.2)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/in VitroDiagnosticsucm301431.htm. An FDA-approved test for the detection of ROS1 rearrangements in NSCLC is not currently available. Refer to Section 14.2 for information on the tests used in the clinical study to identify patients with ROS1 rearrangements in NSCLC.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

14 CLINICAL STUDIES

14.2 ROS1-Positive Metastatic NSCLC

The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older.

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**Table of Pharmacogenomic Biomarkers in Drug Labeling**

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<td>202806, 05/04/2018</td>
<td>Dabrafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage</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)]. 1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)]. 1.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma TAFINLAR is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see Dosage and Administration (2.1), (2.3)]. 1.4 BRAF V600E Mutation-Positive Metastatic NSCLC TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.4)]. 1.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)]. 1.6 Limitations of Use TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC [see Warnings and Precautions (5.2)].</td>
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<td>2.1 Patient Selection</td>
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<td>• 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)].</td>
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<td>• 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)].</td>
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</table>
|                                        |      |                  |            |                  | • Information on FDA-approved tests for the detection of BRAF V6000 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 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.
ATC |
|                                        |      |                  |            |                  | • 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 556 patients with BRAF V6000 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). |

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<tr>
<td>Metastatic or Unresectable BRAF V600 Mutation Positive Melanoma</td>
<td>TAFINLAR as a Single Agent</td>
<td></td>
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<td>Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of the BREAK-3 study (see Clinical Studies (14.1)). This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m² intravenously every 3 weeks (n = 63). (…) TAFINLAR Administered with Trametinib The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma who received TAFINLAR in two trials, Trial 2 (n = 205) 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. (…) Adjacent Treatment of BRAF V600E or V600K Mutation-Positive Melanoma The safety of TAFINLAR when administered with trametinib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study (see Clinical Studies (14.3)). (…) Metastatic, BRAF V600E-Mutation Positive, Non-Small Cell Lung Cancer (NSCLC) The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF1313928). (…) Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC) The safety of TAFINLAR when administered with trametinib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF171019). (…)</td>
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12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics Cardiac Electrophysiology The potential effect of TAFINLAR on QT prolongation was assessed in a dedicated multiple-dose study in 32 patients with BRAF V600 mutation-positive tumors. No large changes in the mean QT interval (i.e., >20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage). (…) |

14 CLINICAL STUDIES
14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent In the BREAK-3 study (NCT01227888), the safety and efficacy of TAFINLAR as a single agent were demonstrated in an international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. (…) All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (67%) were tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF assay. (…) In supportive analyses based on an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis. The safety and efficacy of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multicenter trial. (See Table 12) (…) |

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; NCT01597968). The COMBI-d study compared TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or TAFINLAR 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 and additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR). The COMBI-v study compared TAFINLAR and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1. (…) All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations. (…) In the COMBI-v study, 704 patients were randomized to TAFINLAR plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91 years), 96% were White, and 55% were male. 6% percent of patients had Stage IIIc, 61% had M1c disease, 67% had a normal LDH, 70% had EGOG performance status of 0, 85% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases. (See Table 13 and Figures 2, 3) |

14.3 Adjacent Treatment of BRAF V600E or V600K Mutation-Positive Melanoma COMBI-AD (NCT 01662083) was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations as detected by the THxID™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or two placebos for up to 1 year. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable in-transit metastases. |

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<td>Oncology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions, Patient Counseling Information</td>
<td>distant metastatic disease, or prior systemic anticancer treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIIA, IIIB, or IIIC). In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range 18-89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIB (41%), Stage IIIC (40%), stage unknown (1%), BRAF V600E mutation (91%), BRAF V600K mutation (9%), macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 14) (…) In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range 18-89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIB (41%), Stage IIIC (40%), stage unknown (1%), BRAF V600E mutation (91%), BRAF V600K mutation (9%), macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 14) (…) 14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC) (…) In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range 18-89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 14) (…) 14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC) In Study BRF113928 (NCT01366343), the safety and efficacy of TAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK-inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). (…) In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 15. (See Table 15) 14.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer (ATC) The safety and efficacy of TAFINLAR administered with trametinib was evaluated in Study BRF117019 (NCT02034110), an activity estimating, nine-cohort, multi-center, non-randomized, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication; who received prior treatment with BRAF or MEK inhibitors; with symptomatic or untreated CNS metastases; or who had airway obstruction. (…) 17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients of the following: Confirmation of BRAF V600 mutation • TAFINLAR as a single agent: Evidence of BRAF V600E mutation in the tumor specimen using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)]. • TAFINLAR with trametinib: Evidence of BRAF V600 mutation in tumor specimens using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)]. (…) 5 WARNINGS AND PRECAUTIONS 5.9 Glucose-6-Phosphate Dehydrogenase Deficiency TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Metastatic or Unresectable BRAF V600E or V600K Mutation-Positive Melanoma (…) In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 15. (See Table 15) 17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide). 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Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Metastatic or Unresectable BRAF V600E or V600K Mutation-Positive Melanoma TAFINLAR as a Single Agent Table 3 and Table 4 present adverse drug reactions identified from analyses of the BREAK-3 study [see Clinical Studies (14.1)]. This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 167) or dacarbazine 1,000 mg/m2 intravenously every 3 weeks (n = 63). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥ Grade 2), corrected QT interval greater than or equal to 480 milliseconds on electrocardiogram, or a known history of glucose-6-phosphate dehydrogenase deficiency. (…) 17 PATIENT COUNSELING INFORMATION Glucose-6-phosphate dehydrogenase (G6PD) deficiency TAFINLAR may cause hemolytic anemia in patients with G6PD deficiency. Advise patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis [see Warnings and Precautions (5.9)]. 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. 5 WARNINGS AND PRECAUTIONS 5.1 New Primary Malignancies Non-Cutaneous Malignancies Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. In the COMBI-d study, non-cutaneous malignancies occurred in 1.4% (3/209) of patients receiving TAFINLAR with trametinib and in 2.8% (6/211) of patients receiving single-agent TAFINLAR. In Study BRF113928, noncutaneous malignancies occurred in 1.1% (1/93) of patients receiving TAFINLAR with trametinib. Monitor patients receiving TAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies [see Dosage and Administration (2.3)].</td>
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<td>14.2 Clinical Trials in HCV Genotype 3 (ALLY-3)</td>
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<td>(…) The 152 treated subjects in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the subjects were male; 90% were white, 5% were Asian, and 4% were black. Most subjects (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype. SVR12 and outcomes in subjects without SVR12 in ALLY-3 are shown by patient population in Table 13. SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B allele status, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4) (…).</td>
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<td>(…) Most subjects (80%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 16% of the subjects had compensated cirrhosis, and 73% had IL28B rs12979860 non-CC genotype. (…) SVR12 rates were comparable regardless of antiretroviral therapy, HCV treatment history, age, race, gender, IL28B allele status, HCV genotype 1 subtype, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4) (…).</td>
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<td>VIZIMPRO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test [see Dosage and Administration (2.1)].</td>
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<td>Select patients for the first-line treatment of metastatic NSCLC with VIZIMPRO based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: <a href="http://www.fda.gov/CompanionDiagnos">http://www.fda.gov/CompanionDiagnos</a></td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>(…) The data in the Warnings and Precautions section reflect exposure to VIZIMPRO in 394 patients with first-line or previously treated NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations who received VIZIMPRO at the recommended dose of 45 mg once daily in 4 randomized, active-controlled trials [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), and Study A7471028 (N=16)] and one single-arm trial [Study A7471017 (N=30)]. The median duration of exposure to VIZIMPRO was 10.8 months (range 0.07-68) [see Warnings and Precautions (5)].</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.5 Geriatric Use</td>
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<td>Of the total number of patients (N=394) in five clinical studies with EGFR mutation-positive NSCLC who received VIZIMPRO at a dose of 45 mg orally once daily [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), Study A7471028 (N=16), and Study A7471017 (N=30)] 40% were 65 years of age and older. (…)</td>
</tr>
<tr>
<td>021794, 07/09/2015</td>
<td>Dapsone (1)</td>
<td>Dermatology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Use in Specific Populations</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.2 Hematologic Effects</td>
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<td>Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6 phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.</td>
</tr>
</tbody>
</table>

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Some subjects with G6PD deficiency using ACZONE® Gel developed laboratory changes suggestive of hemolysis. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel, 5%, including patients who were G6PD deficient. Discontinue ACZONE® Gel, 5%, if signs and symptoms suggestive of hemolytic anemia occur. Avoid use of ACZONE® Gel, 5%, in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of ACZONE® Gel, 5%, with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

8 USE IN SPECIFIC POPULATIONS
8.6 G6PD Deficiency
ACZONE® Gel, 5% and vehicle were evaluated in a randomized, double-blind, cross-over design clinical study of 64 patients with G6PD deficiency and acne vulgaris. Subjects were Black (88%), Asian (6%), Hispanic (2%) or of other racial origin (5%). Blood samples were taken at Baseline, Week 2, and Week 12 during both vehicle and ACZONE® Gel, 5% treatment periods. There were 56 out of 64 subjects who had a Week 2 blood draw and applied at least 50% of treatment applications. Table 3 contains results from testing of relevant hematology parameters for these two treatment periods. ACZONE® Gel was associated with a 0.32 g/dL drop in hemoglobin after two weeks of treatment, but hemoglobin levels generally returned to baseline levels at Week 12. (See Table 3)

There were no changes from baseline in aspartate aminotransferase or alanine transaminase during ACZONE® or vehicle treatment at either the 2-week or 12-week time point. The proportion of subjects who experienced decreases in hemoglobin ≥1 g/dL was similar between ACZONE® Gel, 5% and vehicle treatment (8 of 58 subjects had such decreases during ACZONE® treatment compared to 7 of 56 subjects during vehicle treatment among subjects with at least one on-treatment hemoglobin assessment). Subgroups based on gender, race, or G6PD enzyme activity did not display any differences in laboratory results from the overall study group. There was no evidence of clinically significant hemolytic anemia in this study. Some of these subjects developed laboratory changes suggestive of hemolysis.

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

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

021794, 07/09/2015
Dapsone (2) Dermatology Nonspecific (Congenital Methemoglobinemia) Warnings and Precautions

088841
Dapsone (3) Infectious Diseases G6PD Precautions, Adverse Reactions, Overdosage Labeling not electronically available at Drugs@FDA

021513, 03/15/2012
Darifenacin Urology CYP2D6 Clinical Pharmacology 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics
Electrophysiology

The effect of six-day treatment of 15 mg and 75 mg Enablex on QT/QTc interval was evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44 percent male, 56 percent female) aged 18 to 65. Subjects included 18 percent poor metabolizer (PMs) and 82 percent extensive metabolizer (EMs). The QT interval was measured over a 24-hour period both predosing and at steady-state. The 75 mg Enablex dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, Enablex did not result in QT/QTc interval prolongation at any time during the steadiestate, which is consistent with baseline QTcF of about 7.8 msec when compared to placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the clinical efficacy and safety studies, the change in median HR following treatment with Enablex was no different from placebo.

12.3 Pharmacokinetics
Absorption

After oral administration of Enablex to healthy volunteers, peak plasma concentrations of darifenacin are reached approximately seven hours after multiple dosing and steady-state plasma concentrations are achieved by the sixth day of dosing. The mean (SD) steady-state time course of Enablex 7.5 mg and 15 mg extended-release tablets is depicted in Figure 1. A summary of mean (standard deviation, SD) steady-state pharmacokinetic parameters of Enablex 7.5 mg and 15 mg extended-release tablets in EMs and PMs of CYP2D6 is provided in Table 3. The mean oral bioavailability of Enablex in EMs at steady-state is estimated to be 15 percent and 19 percent for 7.5 mg and 15 mg tablets, respectively. (See Figure 1 and Table 3)

Variability in Metabolism
A subset of individuals (approximately 7 percent Caucasians and 2 percent African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM versus EM) for Cmax and AUC following darifenacin 15 mg once daily at steady-state were 1.9 and 1.7, respectively. Excretion
Following administration of an oral dose of 14C-darifenacin solution to healthy volunteers, approximately 60 percent of the radioactivity was recovered in the urine and 40 percent in the feces. Only a small percentage of the excreted dose was unchanged darifenacin (3 percent). Estimated darifenacin clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life of darifenacin following chronic dosing is approximately 13 to 19 hours.

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Blue text represents the most recent additions and/or changes since last posted version.
| NDA/ANDA/BLA Number, Label Version Date | Drug | Therapeutic Area | Biomarker | Labeling Sections | Labeling Text
|----------------------------------------|------|-----------------|-----------|------------------|-----------------
| 206819, 02/14/2017                      | Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | In clinical studies of adult CML patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

14 CLINICAL STUDIES 14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis Subjects with Chronic HCV GT1a Infection without Cirrhosis Subjects with HCV GT1a infection without cirrhosis treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHERINE-I and -II and in PEARL-IV [see Clinical Studies (14.1)]. Subjects had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 19% had a body mass index of at least 30 kg/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/mL; (…)

14.1 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/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/mL; 69% had HCV GT1a infection; 31% had HCV GT1b infection; 42% were treatment-naïve, 36% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders; 14% were prior pegIFN/RBV relapsers; 15% had platelet counts of less than 90 x 10⁹/L; 50% had albumin less than 3.5 g/dL; (…)

14.6 Clinical Trial in Subjects with HCV/HIV-1 Co-infection (TURQUOISE-I) (…) Treated subjects had a median age of 51 years (range: 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/m²; 40% of patients were enrolled in US sites; 22% had platelet counts of less than 90 x 10⁹/L; 17% had albumin less than 3.5 g/L; 92% had baseline HCV RNA levels of at least 800,000 IU/mL; 83% had IL28B (rs12979860) non-CC genotype; (…)

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

5.3 Fluid Retention

(...

6 ADVERSE REACTIONS

(...

6.2 Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

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. (...)

6.3 Additional Pooled Data From Clinical Trials

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

14 CLINICAL STUDIES

(...

14.1 Study 1: Placebo Controlled Study in CTCL (Stage la to III Patients)

The safety and efficacy of Ontak were evaluated in a randomized, double-blind, placebo-controlled, 3-arm trial in patients with Stage Ia to III CD25(+) CTCL. Eligible patients were required to have expression of CD25 on ≥20% of biopsied malignant cells by immunohistochemistry [see Warnings and Precautions (5.4)] (...)

14.2 Study 2: Dose Evaluation Study in CTCL (Stage IIb to IVa) Patients

Confirm that the patient’s malignant cells expressCD25 prior to administration of Ontak. A testing service for the assay of CD25 expression in tumor biopsy samples is available.

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 IL-2 receptor [see Warnings and Precautions (5.4)].

5 WARNINGS AND PRECAUTIONS

5.4 CD25 Tumor Expression and Evaluation

Confirm that the patient’s malignant cells expressCD25 prior to administration of Ontak. A testing service for the assay of CD25 expression in tumor biopsy samples is available.

14 CLINICAL STUDIES

14.1 Study 1: Placebo Controlled Study in CTCL (Stage la to III Patients)

The safety and efficacy of Ontak were evaluated in a randomized, double-blind, placebo-controlled, 3-arm trial in patients with Stage Ia to III CD25(+) CTCL. Eligible patients were required to have expression of CD25 on ≥20% of biopsied malignant cells by immunohistochemistry [see Warnings and Precautions (5.4)] (...)

14.2 Study 2: Dose Evaluation Study in CTCL (Stage IIb to IVa) Patients

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</thead>
<tbody>
<tr>
<td>014399, 07/02/2014</td>
<td>Desipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>A randomized, double-blind study was conducted to evaluate doses of 9 or 18 mcg/kg/day in 71 patients with recurrent or persistent, Stage llb to IVa CTCL. Entry to this study required demonstration of CD25 expression on at least 20% of the cells in any relevant tumor tissue sample (skin biopsy) or circulating cells. Tumor biopsies were not evaluated for expression of other IL-2 receptor subunits (CD122/CD132).</td>
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<tr>
<td>020118, 11/04/2016</td>
<td>Desflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS The use of SUPRANE is contraindicated in the following conditions:</td>
</tr>
<tr>
<td>021992, 12/19/2017</td>
<td>Desvenlafaxine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and elimination Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT 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.</td>
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<tr>
<td>208082, 04/03/2017</td>
<td>Deutetrabenazine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.4 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)].</td>
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<tr>
<td>022287, 10/24/2016</td>
<td>Dexlansoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.</td>
</tr>
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</table>

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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>021879, 01/20/2015</td>
<td>Dextromethorphan and Quinidine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
<td>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.</td>
</tr>
<tr>
<td>020648, 12/16/2016</td>
<td>Diazepam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Concomitant use of CYP2D6 Substrates The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 [see Drug Interactions (7.5)]. 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.</td>
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<tr>
<td>125516, 03/10/2015</td>
<td>Dinutuximab</td>
<td>Oncology</td>
<td>MYCN</td>
<td>Clinical Studies</td>
<td>5 WARNINGS AND PRECAUTIONS 5.4 Concomitant use of CYP2D6 Substrates The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 [see Drug Interactions (7.5)]. 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 [see Warnings and Precautions (5.4), (5.8), and Clinical Pharmacology (12.3)].</td>
</tr>
<tr>
<td>022234, 09/24/2018</td>
<td>Docetaxel</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination NUEDEXTA is a combination product containing dextromethorphan and quinidine. Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. After dextromethorphan 30 mg/quinidine 30 mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours. (…)</td>
</tr>
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</thead>
</table>
| 204790, 06/09/2016                     | Dolutegravir | Infectious Diseases | UGT1A1 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  12.3 Pharmacokinetics  
Metabolism and Elimination  
Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 43). |
| 020690, 12/18/2018                     | Donepezil | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  12.3 Pharmacokinetics  
Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isozymes 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 6-0-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. |
| 022036, 03/17/2010                     | Doxepin (1) | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  12.5. Special Population  
Poor Metabolizers of CYPs  
Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects. |
| 022036, 03/17/2010                     | Doxepin (2) | Psychiatry | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  12.5. Special Population  
Poor Metabolizers of CYPs  
Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects. |
| 205525, 07/01/2016                     | Dronabinol | Gastroenterology | CYP2C9 | Use in Specific Populations, Clinical Pharmacology | 8 USE IN SPECIFIC POPULATIONS  8.6 Effect of CYP2C9 Polymorphism  
Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function (see Clinical Pharmacology (12.5)). |
| 021676, 06/01/2015                     | Drospirenone and Ethinyl Estradiol | Gynecology | CYP2C19 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  12.3 Pharmacokinetics  
Effects of Combined Oral Contraceptives on Other Drugs  
(…) In the study with 24 postmenopausal women (including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotypes), 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. (…) |
| 021427, 01/04/2017                     | Duloxetine | Psychiatry | CYP2D6 | Drug Interactions | 7 DRUG INTERACTIONS  7.3 Dual inhibition of CYP1A2 and CYP2D6  
Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax. |
| 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 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status had no clinically significant effect on the pharmacokinetics of durvalumab. (…) |
| 211155, 06/24/2018                     | Duvelisib | Oncology | Chromosome 17q | Clinical Studies | 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 6) (…) |

* Therapeutic areas do not necessarily reflect the CDER review division.  
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<tr>
<td>020972, 01/30/2017</td>
<td>Efavirenz</td>
<td>Infectious Diseases</td>
<td>CYP2B6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Cardiac Electrophysiology The effect of 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 56 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6*6/<em>6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6</em>1/<em>1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval were 8.7 ms and 11.3 ms in subjects with CYP2B6</em>6/*6 genotype following the administration of 600 mg daily dose for 14 days [see Warnings and Precautions (5.2)].</td>
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<tr>
<td>210440, 07/23/2018</td>
<td>Elagolix</td>
<td>Gynecology</td>
<td>SLCO1B1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Disposition of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in groups of patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T&gt;C). 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 [i.e., SLCO1B1 521T/T] phenotype.</td>
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<tr>
<td>208261, 02/14/2017</td>
<td>Ebsenziv and Grazoprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE COINFECTION) (...). C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naïve subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized in a 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-naïve HCV/HIV-1 coinfected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks. Among subjects with genotype 1 infection, the median age was 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. (...).</td>
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<td>14.3 Clinical Trials in Treatment-Experienced Subjects with Genotype 1 HCV Treatment-Experienced Subjects who Failed Prior PegIFN + RBV Therapy (C-EDGE TE) (...). C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1 ratio to one of the following treatment groups: ZEPATIER for 12 weeks, ZEPATIER + RBV for 12 weeks, or ZEPATIER 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. (...).</td>
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<td>14.4 Clinical Trial in Subjects with Genotype 1 HCV and Severe Renal Impairment including Subjects on Hemodialysis (C-SURFER) C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior therapy with IFN or PegIFN ± RBV therapy. Subjects were randomized in a 2:1:1 ratio to one of the following treatment groups: EBR + GZR for 12 weeks, ZEPATIER + RBV for 12 weeks, ZEPATIER for 16 weeks, or ZEPATIER for 12 weeks. Subjects with genotype 1 infection and 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. (...).</td>
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| 205494, 08/29/2018                     | Eliglustat | Inborn Errors of Metabolism | CYP2D6 | Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | **INDICATIONS AND USAGE**  
CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test [see Dosage and Administration (2.1)].  
Limitations of Use:  
• Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect [see Clinical Studies (14)].  
• A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) [see Clinical Studies (14)].  

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

2.2 Recommended Adult Dosage  
The recommended dosage of CERDELGA in adults is based on the patient’s CYP2D6 metabolizer status. (See Table 1)  

2.3 Dosage Adjustment in EMs and IMs With or Without Hepatic Impairment and Concomitant Use of CYP2D6 or CYP3A Inhibitors  
Reduce dosage frequency of CERDELGA 84 mg to once daily in CYP2D6 EMs and IMs with or without hepatic impairment taking CYP2D6 or CYP3A inhibitors, as shown in Table 2 [see Warnings and Precautions (5.1), Drug Interactions (7.1), Use in Specific Populations (8.7)]. (See Table 2)  

4 CONTRAINDICATIONS  
CERDELGA is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals.  
EMs  
• Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [see Drug Interactions (7.1)]  
• Moderate or severe hepatic impairment [see Use in Specific Populations (8.7)]  
• Mild hepatic impairment and taking a strong or moderate CYP2D6 inhibitor [see Use in Specific Populations (8.7)]  
IMs  
• Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [see Drug Interactions (7.1)]  
• Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)]  
• Any degree of hepatic impairment [see Use in Specific Populations (8.7)]  
PMs  
• Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)]  
• Any degree of hepatic impairment [see Use in Specific Populations (8.7)]  

5 WARNINGS AND PRECAUTIONS  
5.1 ECG Changes and Potential for Cardiac Arrhythmias  
CERDELGA is predicted to cause increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations and may increase the risk of cardiac arrhythmias.  
• Use of CERDELGA is contraindicated, to be avoided, or requires dosage adjustment in patients taking CYP2D6 or CYP3A inhibitors, depending CYP2D6 metabolizer status, type of inhibitor, or degree of hepatic impairment [see Dosage and Administration (2.3), Contraindications (4), Drug Interactions (7.1)]. (…)  

6 DRUG INTERACTIONS  
7.1 Effect of Other Drugs on CERDELGA  
Co-administration of CERDELGA with:  
• CYP2D6 or CYP3A inhibitors may increase eliglustat concentrations which may increase the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac interval [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)].  
• Strong CYP3A inducers decreases eliglustat concentrations which may reduce CERDELGA efficacy [see Clinical Pharmacology (12.3)].  

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)].  
Eldad  
• 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)  

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2018**

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<td>IMS and PMs</td>
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<td>• Avoid CERDELGA in patients with any degree of renal impairment.</td>
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<td>8.7 Hepatic Impairment</td>
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<td>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)].</td>
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<td>IMSs</td>
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<td>• CERDELGA is contraindicated in patients with [see Contraindications (4)]: o severe (Child-Pugh Class C) hepatic impairment o moderate (Child-Pugh Class B) hepatic impairment o mild (Child-Pugh Class A) hepatic impairment taking a strong or moderate CYP2D6 inhibitor</td>
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<td>• Reduce dosage frequency of CERDELGA 84 mg to once daily [see Dosage and Administration (2.3)] in patients with mild hepatic impairment taking: o a weak CYP2D6 inhibitor o a strong, moderate, or weak CYP3A inhibitor</td>
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<td>• No dosage adjustment is recommended in patients with mild hepatic impairment, unless otherwise specified above.</td>
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<td>PMs</td>
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<td>• CERDELGA is contraindicated in patients with any degree of hepatic impairment [see Contraindications (4)].</td>
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</table>

### 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.

**Dosage of CERDELGA**

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

Table 7 describes the pharmacokinetic parameters for eliglustat in healthy subjects following multiple doses of 84 mg CERDELGA twice daily. (See Table 7)

### Administration

Administration of CERDELGA with a high fat meal (approximately 1000 calories with 50% calories from fat) resulted in a 15% decrease in Cmax (not clinically significant) but no change in AUC.

### Distribution

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

### Elimination

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

### Specific Populations

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

### Patients with renal impairment

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

### Patients with hepatic impairment

Eliglustat pharmacokinetics in CYP2D6 EMs with mild and moderate hepatic impairment is unknown [see Use in Specific Populations (8.7)].

### Effect of other drugs on CERDELGA

**CYP2D6 substrates**

Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage), metoprolol (a CYP2D6 substrate) mean Cmax and AUC increased by 1.7-fold and 2.3-fold in CYP2D6 EMs, respectively, and by 1.2-fold and 1.6-fold in IMs, respectively [see Drug Interactions (7.1)].

**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)].

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| 125460, 02/14/2014                      | Elsulfase | Inborn Errors of Metabolism | GALNS | Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
Vimizim (elsulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).  

5 WARNINGS AND PRECAUTIONS  
5.2 Risk of Acute Respiratory Complications  
Patients with acute febrile or respiratory illness at the time of Vimizim infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient’s clinical status prior to administration of Vimizim and consider delaying the Vimizim infusion.  
Sleep apnea is common in MPS IVA patients. Evaluation of airway patency should be considered prior to initiation of treatment with Vimizim. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an acute reaction, or extreme drowsiness/sleep induced by antihistamine use.  

5.3 Spinal or Cervical Cord Compression  
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.  

1 USE IN SPECIFIC POPULATIONS  
8.3 Nursing Mothers  
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. (…)  
14 CLINICAL STUDIES  
The pharmacokinetics of elosulfase 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. (…)  

14/12/2016 | Eltrombopag (1) | Hematology | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.3 Thrombotic/Thromboembolic Complications  
Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included 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). (…)  

14 CLINICAL STUDIES  
A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FH3-UNC13D (MUNC 13-4) (26%), PHIL2-PRF1 (19%), and Griscelli Syndrome type 2 (19%). The HLH mutations in the population enrolled are described in Table 3. (See Table 3)  

022291, 10/12/2016 | Eltrombopag (2) | Hematology | SERPINC1 (Antithrombin III) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS  
5.3 Thrombotic/Thromboembolic Complications  
Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). (…)  

022291, 10/12/2016 | Emapalumab-lzsg | Hematology | PRF1, RAB27A, SHZD1A, STXBP2, STX11, UNC13D, XIAP (Hemophagocytic Lymphohistiocytic syndrome) | Clinical Studies | 14 CLINICAL STUDIES  
A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FH3-UNC13D (MUNC 13-4) (26%), PHIL2-PRF1 (19%), and Griscelli Syndrome type 2 (19%). The HLH mutations in the population enrolled are described in Table 3. (See Table 3)  

761107, 11/20/2018 | Enasidenib | Oncology | IDH2 | Indications and Usage, Dosage and Administration | 1 INDICATIONS AND USAGE  
1.1 Acute Myeloid Leukemia  
IDHIFA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.  

209806, 08/01/2017 | | | | |

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<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>2 INDICATIONS AND USAGE 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>
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2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI [see Indications and Usage (1), Dosage and Administration (2.1)]. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics. |

5 WARNINGS AND PRECAUTIONS

5.2 Tumor Promotion in BRAF Wild-Type Tumors

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

(...)

6.2 Other Adverse Reactions

(...)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib were observed in elderly patients as compared to younger patients [see Clinical Pharmacology (12.3)]. |

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

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

14 CLINICAL STUDIES

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<th>Labeling Sections</th>
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<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>
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<td>201532, 10/19/2016</td>
<td>Erbitux (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES: 14.1 Metastatic Breast Cancer: Randomization was stratified by geographic region, HER2/neu status, and prior capecitabine exposure. HALAVEN was administered at a dose of 1.4 mg/m² on Days 1 and 8 of a 21-day cycle. HALAVEN-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 16% gemcitabine, 16% capcitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), and 3% hormonal therapy. The main efficacy outcome was overall survival: (…) Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER-, PR-, HER2/neu+), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (…)</td>
</tr>
<tr>
<td>201532, 10/19/2016</td>
<td>Erbitux (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES: 14.1 Metastatic Breast Cancer: (…) Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER-, PR-, HER2/neu+), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (…)</td>
</tr>
<tr>
<td>021743, 10/18/2016</td>
<td>Erlotinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE: 1.1 Non-Small Cell Lung Cancer (NSCLC): TARCEVA® is indicated for: • The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen [see Clinical Studies (14.1, 14.3)]. Limitations of use: • Safety and efficacy of TARCEVA have not been established in patients with NSCLC whose tumors have other EGFR mutations [see Clinical Studies (14.1, 14.2)].</td>
</tr>
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<tr>
<td>BRAFV600E</td>
<td>Area</td>
<td>Contraindications</td>
<td>CONTRAINDICATIONS: (…) Based on centralized testing, 100% of patients’ tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (&lt;1%) (…)</td>
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</table>

BRAFV600 in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux ThermoB® BRAF assay. (…) Based on centralized testing, 100% of patients’ tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%) (…) |
Table of Pharmacogenomic Biomarkers in Drug Labeling
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<td>G6PD</td>
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<td>Labeling not electronically available on Drugs@FDA</td>
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<td>Escitalopram (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
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<tr>
<td>021323, 01/04/2017</td>
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<td>022101, 12/20/2016</td>
<td>Esomeprazole</td>
<td>Gastroenterology</td>
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<td>Drug Interactions, Clinical Pharmacology</td>
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<tr>
<td>206488, 09/19/2016</td>
<td>Eteplirsen</td>
<td>Neurology</td>
<td>DMD</td>
<td>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td></td>
</tr>
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(…) The disease characteristics were 93% Stage IV and 7% Stage IIIb with pleural effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition). 93% adenocarcinoma, 66% exon 19 mutation deletions and 34% exon 21 (L858R) point mutation by CTA. (…) In exploratory subgroup analyses based on EGFR mutation subtype, the hazard ratio (HR) for PFS was 0.27 (95% CI 0.17 to 0.43) in patients with exon 19 deletions and 0.52 (95% CI 0.29 to 0.95) in patients with exon 21 (L858R) substitution. The HR for OS was 0.94 (95% CI 0.57 to 1.54) in the exon 18 deletion subgroup and 0.98 (95% CI 0.66 to 1.76) in the exon 21 (L858R) substitution subgroup. 14.2 NSCLC – Lack of Efficacy of TARCEVA in Maintenance Treatment of Patients without EGFR Mutations Lack of efficacy of TARCEVA for the maintenance treatment of patients with NSCLC without EGFR activating mutations was demonstrated in Study 2. Study 2 was a multicenter, placebo-controlled, randomized trial of 643 patients with advanced NSCLC without an EGFR exon 19 deletion or exon 21 L858R substitution mutation who had not experienced disease progression after four cycles of platinum-based chemotherapy. (…) 14.3 NSCLC – Maintenance Treatment or Second/Third Line Treatment Two randomized, double-blind, placebo-controlled trials, Studies 3 and 4, examined the efficacy and safety of TARCEVA administered to patients with metastatic NSCLC as maintenance therapy after initial treatment with chemotherapy (Study 3) or with disease progression following initial treatment with chemotherapy (Study 4). Determination of EGFR mutation status was not required for enrollment. (…) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including bronchioloalveolar (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…) 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. (…) 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 was 6.6 (7.9) msc. 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 dose of 30 mg is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg. 7 DRUG INTERACTIONS 7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways (…) Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. 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 metabolizers (Cmax and AUC decreased by 49.6 % and 43.9%, respectively). Avoid concomitant use of St. John’s Wort or rifampin with NEXIUM. 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

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</table>
| 022334, 06/14/2016                     | Everolimus (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Studies | 14 CLINICAL STUDIES

**EXONDYS 51** was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. (…)

### 1 INDICATIONS AND USAGE

1.1 **Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)**

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

2.1 **Recommended Dose in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced NET, Advanced RCC, and Renal Angiomyolipoma with TSC**

The recommended dose of AFINITOR Tablets is 10 mg, to be taken once daily at the same time every day. (…)

2.2 **Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced NET, Advanced RCC, and Renal Angiomyolipoma with TSC**

Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction of AFINITOR therapy) or discontinuation. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered [see Warnings and Precautions (5)]. (…)

### 5 WARNINGS AND PRECAUTIONS

5.7 **Geriatric Patients**

In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [see Dosage and Administration (2.2), Use in Specific Populations (8.5)]. (…)

### 6 ADVERSE REACTIONS

6.1 **Clinical Study Experience in Advanced Hormone Receptor-Positive, HER2 Negative Breast Cancer**

The efficacy and safety of AFINITOR (10 mg/day) plus exemestane (25 mg/day) (n=485) versus placebo plus exemestane (25 mg/day) (n=239) was evaluated in a randomized, controlled trial in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (range 28-95 years), and 75% were Caucasian. Safety results are based on a median follow-up of approximately 13 months. (…)

### 7 DRUG INTERACTIONS

7.3 **Drugs That May Have Their Plasma Concentrations Altered by Everolimus**

(…) No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination. (…)

### 8 USE IN SPECIFIC POPULATIONS

8.5 **Geriatric Use**

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness were observed between elderly and younger patients. (…)

### 14 CLINICAL STUDIES

14.1 **Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer**

A randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (…)

| 022334, 06/14/2016                     | Everolimus (2) | Oncology | ESR (Hormone Receptor) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE

1.1 **Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)**

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

2.1 **Recommended Dose in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced NET, Advanced RCC, and Renal Angiomyolipoma with TSC**

The recommended dose of AFINITOR Tablets is 10 mg, to be taken once daily at the same time every day. (…)

2.2 **Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced NET, Advanced RCC, and Renal Angiomyolipoma with TSC**

Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction of AFINITOR therapy) or discontinuation. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered [see Warnings and Precautions (5)]. (…)

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<td>020753, 05/18/2018</td>
<td>Exemestane</td>
<td>Oncology</td>
<td>ESR, PGR</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction of AFINITOR therapy) or discontinuation. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered (see Warnings and Precautions (5)). (…)</td>
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<tr>
<td>022030, 11/21/2017</td>
<td>Fesoterodine</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>5 WARNINGS AND PRECAUTIONS 5.7 Geriatric Patients In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients &lt; 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients &lt; 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended (see Dosage and Administration (2.2), Use in Specific Populations (8.5)). (…)</td>
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| 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 CYP2C19 Metabolizers  
In a pharmacogenic study of 100 mg ADDYI in subjects who were poor or extensive CYP2C19 metabolizers, syncope occurred in 1/9 (11%) subjects who were CYP2C19 poor metabolizers (this subject had a 3.2 fold higher flibanserin exposure compared to CYP2C19 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C19 extensive metabolizers [see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)].  
8 USE IN SPECIFIC POPULATIONS  
8.7 CYP2C19 Poor Metabolizers  
CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer [see Adverse Reactions (6.1) and Clinical Pharmacology (12.5)]. Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians. |
| 022526, 08/18/2015                     | Flibanserin (2) | Gynecology      | CYP2C19    | Adverse Reactions, Use in Specific Populations, 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.  
CYP2C19 Poor Metabolizers  
A study comparing flibanserin exposure in CYP2C19 poor metabolizers to CYP2C19 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C19 inhibitor. In 9 women who were poor metabolizers of CYP2C19, Cmax and AUC0-inf of flibanserin 100 mg once daily increased 1.5-fold (1.1-2.1) and 1.3-fold (0.9-2.1), compared to exposures among 8 extensive metabolizers of CYP2C19. Flibanserin half-life was increased from 11.1 hours in the extensive metabolizers of CYP2C19 to 13.5 hours in the poor metabolizers of CYP2C19 [see Adverse Reactions (6.1) and Use in Specific Populations (8.7)]. The frequencies of poor metabolizers of CYP2C19 are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians. |
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<td>Flibanserin (3)</td>
<td>Gynecology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>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. A study comparing flibanserin exposure in CYP2D6 poor metabolizers to CYP2D6 extensive metabolizers was conducted in addition to a drug interaction study with paroxetine, a strong CYP2D6 inhibitor. In 12 poor metabolizers of CYP2D6, steady state Cmax and AUC of flibanserin 50 mg twice daily was decreased by 4% and increased by 18%, respectively, compared to exposures among 19 extensive metabolizers, intermediate metabolizers and ultra rapid metabolizers of CYP2D6.</td>
</tr>
</tbody>
</table>
| Fluorouracil (1) | Dermatology       | DPD        | Contraindications, Warnings | CONTRAINDICATIONS (…) Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. (…)

**WARNINGS**

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive. 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 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.

| Fluorouracil (2) | Oncology | DPD | 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 postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test. |
| Fluoxetine (3) | Psychiatry | CYP2D6 | Precautions, Clinical Pharmacology | PRECAUTIONS Drugs metabolized by CYP2D6. Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Co-administration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, higher dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (see CONTRAINDICATIONS and WARNINGS). |

**CLINICAL PHARMACOLOGY**

Clinical issues related to metabolism/elimination The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine’s clinical use. Variability in metabolism- A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. (…)

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Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 12/2018

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<tr>
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<tbody>
<tr>
<td>018766, 05/09/2016</td>
<td>Flurbiprofen</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Poor Metabolizers of CYP2C9 Substrates In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.</td>
</tr>
<tr>
<td>018554, 07/23/2001</td>
<td>Flutamide</td>
<td>Oncology</td>
<td>G6PD Warnings</td>
<td>WARNINGS Aniline Toxicity: One metabolite of flutamide is 4-nitro-3-fluoromethylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (e.g., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methemoglobin levels should be considered.</td>
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<tr>
<td>022007, 11/30/2017</td>
<td>Formoterol (1)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.</td>
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<tr>
<td>022007, 11/30/2017</td>
<td>Formoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.</td>
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<tr>
<td>020450, 10/31/2017</td>
<td>Fosphenytoin</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings and Precautions 5.4 Serious Dermatologic Reactions Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin (the active metabolite of CEREBYX) treatment. The onset of symptoms is usually within 28 days, but can occur later. CEREBYX should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.5)]. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA B<em>1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B</em>1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding CEREBYX as an alternative for carbamazepine patients positive for HLA-B<em>1502. The use of HLA-B</em>1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of drug metabolic monitoring have not been studied.</td>
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<tr>
<td>022033, 01/04/2017</td>
<td>Fluvoxamine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>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>
<td></td>
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<tr>
<td>021344, 07/12/2016</td>
<td>Fulvestrant (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage 1 INDICATIONS AND USAGE Combination Therapy with Palbociclib (…) FASLODEX is indicated for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.</td>
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</table>
| Fulvestrant (2) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE  
Monotherapy  
FASLODEX is indicated for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.  
Combination Therapy with Palbociclib  
FASLODEX is indicated for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.  
6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Combination Therapy with Palbociclib  
The safety of FASLODEX (500 mg) plus palbociclib (125 mg/day) versus FASLODEX plus placebo was evaluated in Study 4. 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 Study 4. (…)  
12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation.  
14 CLINICAL STUDIES  
Monotherapy  
Comparison of FASLODEX 500 mg and FASLODEX 250 mg (Study 1)  
(…) The median age of study participants was 61. All patients had ER+ advanced breast cancer. Approximately 30% of subjects had no measurable disease. Approximately 55% of patients had visceral disease. (…)  
Comparison of FASLODEX 250 mg and Anastrozole 1 mg in Combined Data (Studies 2 and 3)  
(…) The median age of study participants was 64. 81.6% of patients had ER+ and/or PgR+ tumors. Patients with ER-/PgR- or unknown tumors were required to have demonstrated a prior response to endocrine therapy. (…)  
Combination Therapy  
FASLODEX 500 mg in Combination with Palbociclib 125 mg (Study 4)  
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 4 was an international, randomized, double-blind, parallel group, multicenter 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. (…) |

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</table>
| Galantamine | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY  
12.3 Pharmacokinetics  
Metabolism and Elimination  
Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine and, inhibitors of both pathways increase oral bioavailability of galantamine modestly. O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In studies of oral 3 H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average. (…)  
(…) RAZADYNE® ER 24 mg extended-release capsules administered once daily under fasting conditions are bioequivalent to RAZADYNE® tablets 12 mg twice daily with respect to AUC24h and Cmin. The Cmax and Tmax of the extended-release tablets, with Cmax about 25% lower and median Tmax occurring about 4.5–5.0 hours after dosing. Dose-proportionality is observed for RAZADYNE® ER extended-release capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER extended-release capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. (…)  
CYP2D6 Poor Metabolizers |

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<td>206995, 07/13/2015</td>
<td>Gefitinib (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% AUC* increase of unchanged galantamine compared to extensive metabolizers. A total of 356 patients with Alzheimer’s disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.</td>
</tr>
<tr>
<td>206995, 07/13/2015</td>
<td>Gefitinib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [see Clinical Studies (14)]. Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations [see Clinical Studies (14)].</td>
</tr>
<tr>
<td>211349, 11/28/2018</td>
<td>Gilteritinib</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.</td>
</tr>
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<td>020496, 12/19/2016</td>
<td>Glimepiride</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS  5.0 Hemolytic Anemia  Sulfonilureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonilurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonilurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving AMARYL who did not have known G6PD deficiency [see Adverse Reactions (6.2)].</td>
</tr>
<tr>
<td>017783, 08/18/2016</td>
<td>Glipizide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS  Hemolytic Anemia  Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonilurea agents can lead to hemolytic anemia. Because GLUCOTROL belongs to the class of sulfonilurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonilurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.</td>
</tr>
<tr>
<td>020051, 05/22/2015</td>
<td>Glyburide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS  Hemolytic Anemia  Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonilurea agents can lead to hemolytic anemia. Because GLYNAS belongs to the class of sulfonilurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonilurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.</td>
</tr>
<tr>
<td>019726, 02/12/2015</td>
<td>Goserelin</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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 (2.0), Clinical Pharmacology (12.1), and Clinical Studies (14.5)].  14 CLINICAL STUDIES  14.5 Breast Cancer  The Southwest Oncology Group conducted a prospective, randomized clinical trial (SWOG-8692 [INT-0075]) in premenopausal women with advanced estrogen receptor positive or progesterone receptor positive breast cancer which compared ZOLADEX with cyclophosphamide. (…) Findings were similar in uncontrolled clinical trials involving patients with hormone receptor positive and negative breast cancer. Premenopausal women with estrogen receptor (ER) status of positive, negative, or unknown participated in the uncontrolled (Phase II and Trial 2302) clinical trials. Objective tumor responses were seen regardless of ER status, as shown in the following table. (See Table 8)</td>
</tr>
<tr>
<td>020727, 04/02/2015</td>
<td>Hydralazine</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</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 three times daily to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-linear kinetics of hydralazine, probably reflecting saturable first pass metabolism. (…)</td>
</tr>
<tr>
<td>009788, 01/27/2017</td>
<td>Hydroxychloroquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS  (…) PLAQUENIL should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…) ADVERSE REACTIONS  Blood and lymphatic system disorders: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…)</td>
</tr>
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| 205552, 01/18/2017                     | Ibrutinib (1) | Oncology | Chromosome 17p | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE  
1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion  
IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [see Clinical Studies (14.2)].  

14 CLINICAL STUDIES  
14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma  
Study 2  
(...). Thirty-two percent of patients had 17p deletion. (...)  
(...). CLL/SLL with 17p deletion (del 17p CLL/SLL) in Study 2  
Study 2 included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 86% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for del 17p CLL/SLL are shown in Table 13. (See Table 13.)  

14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma  
Study 3  
(...). The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%). (...)  

1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor > 5 cm and 26% presented with del11q. (...)  

205552, 01/18/2017 | Ibrutinib (2) | Oncology | Chromosome 11q | Clinical Studies | 14 CLINICAL STUDIES  
14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma  
Study 3  
(...). The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%). (...)  

1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor > 5 cm and 26% presented with del11q. (...)  

022192, 05/26/2016 | Iloperidone | Psychiatry | CYP2D6 | Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology | 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)].  

5 WARNINGS AND PRECAUTIONS  
5.3 QT Prolongation  
(...). Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism [see Drug Interactions (7.1)], and in patients with reduced activity of CYP2D6 [see Clinical Pharmacology (12.3)]. (...)  

7 DRUG INTERACTIONS  
7.1 Potential for Other Drugs to Affect FANAPT  
Fluoxetine: Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 28–44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2– to 3-fold, and decreased the AUC of its metabolite P95 by one-half. (...)  

12.3 Pharmacokinetics  
The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3–4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4.  

Metabolism and Elimination  
Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P86 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. Approximately 7% - 10% of Caucasians and 3% - 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers. Coadministration of FANAPT with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3-fold increase in iloperidone plasma exposure, and therefore one-half of the FANAPT dose should be administered. Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs. The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.  

021588, 09/27/2016 | Imatinib (1) | Oncology | KIT | Indications and Usage, Dosage | 1 INDICATIONS AND USAGE  
1.6 Aggressive Systemic Mastocytosis (ASM)  

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<td>Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test [see Dosage and Administration (2.7)] or with c-Kit mutational status unknown. 1.9 Kit+ Gastrointestinal Stromal Tumors (GIST) Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. 1.10 Adjuvant Treatment of GIST Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.7 Adult Patients with ASM Determine D816 V c-Kit mutation status prior to initiating treatment. Information on FDA-approved test for the detection of D816 V c-Kit mutation 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 ASM without the D816 V c-Kit mutation. If c-Kit mutational status is 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.</td>
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<td>14 CLINICAL STUDIES</td>
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<td>14.5 Myelodysplastic/Myeloproliferative Diseases</td>
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<td>(…) Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I) and four patients had a D816V c-Kit mutation (not considered sensitive to Gleevec), one with concomitant CML.</td>
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<td>(…) Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.</td>
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<td>14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia</td>
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<td>14.8 Dermatofibrosarcoma Protubersans</td>
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<td>14.9 Gastrointestinal Stromal Tumors</td>
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<td>(…) One open-label, multinational Phase 2 study was conducted in patients with Kit (CD117) positive unresectable or metastatic malignant GIST.</td>
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<td>(…) Adjuvant Treatment of GIST</td>
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<td>In the adjuvant setting, Gleevec was investigated in a multicenter, double-blind, placebo-controlled, randomized trial involving 713 patients (Study 1). Patients were randomized one to one to Gleevec at 400 mg/day or matching placebo for 12 months. The ages of these patients ranged from 18 to 91 years. Patients were included who had a histologic diagnosis of primary GIST, expressing KIT protein by immunohistochemistry and a tumor size greater than or equal to 3 cm in maximum dimension with complete gross resection of primary GIST within 14 to 70 days prior to registration.</td>
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<td>(…) A second randomized, multicenter, open-label, phase 3 trial in the adjuvant setting (Study 2) compared 12 months of Gleevec treatment to 36 months of Gleevec treatment at 400 mg/day in adult patients with Kit (CD117) positive GIST after surgical resection with one of the following: tumor diameter greater than 5 cm and mitotic count greater than 5/50 high power fields (HPF), or tumor diameter greater than 10 cm and any mitotic count, or tumor of any size with mitotic count greater than 10/50 HPF, or tumors ruptured into the peritoneal cavity.</td>
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<td>021588, 09/27/2016</td>
<td>Imatinib (2)</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
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<td>1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)</td>
<td>Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. 1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alfa (IFN) Therapy Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.</td>
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<td>1.3 Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)</td>
<td>Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia. 1.4 Pediatric patients with Ph+ Acute Lymphoblastic Leukemia (ALL) Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.2 Adult Patients with Ph+CML CP, AP, or BC</td>
<td>The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia.</td>
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|                                        |      |                   |            |                  | thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response. 2.3 Pediatric Patients with Ph+ CML CP The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with Gleevec treatment in children under 1 year of age. 2.4 Adult Patients with Ph+ ALL The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL. 2.5 Pediatric Patients with Ph+ ALL The recommended dose of Gleevec to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m²/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose. 2.14 Dose Adjustment for Hematologic Adverse Reactions Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (…) 5 WARNINGS AND PRECAUTIONS 5.1 Fluid Retention and Edema (…) In a randomized trial in patients with newly diagnosed Ph+CML in chronic phase comparing Gleevec and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Gleevec and in 3.9% of patients receiving nilotinib 300 mg bid. (…) 5.3 Congestive Heart Failure and Left Ventricular Dysfunction (…) In an international randomized phase 3 study in 1,108 patients with newly diagnosed Ph+CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. In another randomized trial with newly diagnosed Ph+CML patients in chronic phase that compared Gleevec and nilotinib, cardiac failure was observed in 1.1% of patients in the Gleevec arm and 2.2% of patients in the nilotinib 300 mg bid arm and severe (Grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. (…) 5.5 Hemorrhage (…) Gastrointestinal tumor sites may have been the source of GI hemorrhages. In a randomized trial in patients with newly diagnosed Ph+CML in chronic phase comparing Gleevec and nilotinib, GI hemorrhage occurred in 1.4% of patients in the Gleevec arm, and in 2.9% of patients in the nilotinib 300 mg bid arm. None of these events were Grade 3 or 4 in the Gleevec arm; 0.7% were Grade 3 or 4 in the nilotinib 300 mg bid arm. In addition, gastric antral vascular ectasia has been reported in postmarketing experience. 6 ADVERSE REACTIONS 6.1 Chronic Myeloid Leukemia The majority of Gleevec-treated patients experienced adverse reactions at some time. Gleevec was discontinued due to drug-related adverse reactions in 2.4% of patients receiving Gleevec in the randomized trial of newly diagnosed patients with Ph+CML in chronic phase comparing Gleevec versus IFN-Ara-C, and in 12.5% of patients receiving Gleevec in the randomized trial of newly diagnosed patients with Ph+CML in chronic phase comparing Gleevec and nilotinib. (See Table 3) (…) 6.2 Adverse Reactions in Pediatric Population In combination with multi-agent chemotherapy (…) Patients with Ph+ ALL (n=92) were assigned to receive Gleevec and treated in 5 successive cohorts. Gleevec exposure was systematically increased in successive cohorts by earlier introduction and more prolonged duration. The safety of Gleevec given in combination with intensive chemotherapy was evaluated by comparing the incidence of grade 3 and 4 adverse events, neutropenia (less than 750/mcL) and thrombocytopenia (less than 75,000/mcL) in the 92 patients with Ph+ ALL compared to 65 patients with Ph- ALL enrolled on the trial who did not receive Gleevec. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Gleevec. The protocol included up to 18 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Gleevec and 647 without Gleevec. The adverse events that were reported with a 5% or greater incidence in patients with Ph+ ALL compared to Ph- ALL or with a 1% or greater incidence in cycles of therapy that included Gleevec are presented in Table 8. (See Table 8) (…) 6.4 Acute Lymphoblastic Leukemia The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps and rash. Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb edema. These edemas were reported as Grade 3/4 events in 6.3% of the patients and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec. 6.7 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia The safety profile in the HES/CEL patient population does not appear to be different from the safety profile of Gleevec observed in other hematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia, and anemia. 8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use The safety and effectiveness of Gleevec have been demonstrated in pediatric patients with newly diagnosed Ph+ chronic phase CML and Ph+ ALL [see Clinical Studies (14.2, 14.4)]. There are no data in children under 1 year of age.

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<td>PDGFRB</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)].

2 DOSAGE AND ADMINISTRATION

2.6 Adult Patients with MDS/MPD

Determine PDGFRβ gene rearrangements status prior to initiating treatment. Information on FDA-approved tests for the detection of PDGFRβ rearrangements is available at http://www.fda.gov/companiondiagnostics.

The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.

14 CLINICAL STUDIES

14.5 Myelodysplastic/Myeloproliferative Diseases

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

Sixteen patients had a translocation, involving chromosome 5q33 or 4q12, resulting in a PDGFR gene rearrangement. All of these patients responded hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1 (7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8–26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in

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<td>FIP1L1-PDGFRα</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
<td>responding patients in the published literature. Results are provided in Table 22. Response durations of phase 2 study patients ranged from 141+ days to 457+ days. (See Table 22)</td>
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### 14.6 Aggressive Systemic Mastocytosis

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (See Table 25) (…)

### 14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia

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

### 14.8 Dermatofibrosarcoma Protubersans

Dermatofibrosarcoma Protubersans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22 that results in the fusion of the collagen type 1 alpha 1 gene and the PDGF B gene. An open-label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…)

### 1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)

Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.

#### 2.7 Adult Patients with ASM


The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec: 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

#### 2.8 Adult Patients with HES/CEL

The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-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) (…)

### 12.4 Pharmacogenomics

The pharmacokinetcs of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/TAI7 genotype (low UGT1A1 expression; also referred to as "2B") and the (TA)8, (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.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

| Therapeutic area do not necessarily reflect the CDER review division. amended 2019/09/12 | 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. amended 2019/09/12 | Blue text represents the most recent addtions and/or changes since last posted version. amended 2019/09/12 |
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| 761040, 08/17/2017                      | Valsartan | Oncology | BCR-ABL1 | Clinical Studies | 14 CLINICAL STUDIES
1.2 Unresectable or Refractory Metastatic Melanoma
The safety and efficacy of Valsartan were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094650) 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 Valsartan at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund’s adjuvant (gp100), 137 were randomized to receive Valsartan at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. (…)

| 125377, 07/10/2018                     | Ipilimumab (1) | Oncology | HLA-A | Clinical Studies | 14 CLINICAL STUDIES
1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, or 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.

| 125377, 07/10/2018                     | Ipilimumab (2) | Oncology | Microsatellite Instability, Mismatch Repair | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, or 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.

| 8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma or for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. (…)

### Footnotes:

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### Key Points:

- 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. (…)
- The pharmacodynamic effects of TEGSEDI were evaluated in hATTR amyloidosis patients treated with 284 mg TEGSEDI via subcutaneous injection once weekly. With repeat dosing, the mean percent decreases from baseline in serum TTR from Week 1 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. (…)
Patients enrolled in the YERVOY and nivolumab MSI-H mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks. Patients enrolled in the single-agent nivolumab MSI-H mCRC cohort received nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks. Treatment in both cohorts continued until unaccustomed toxicity or radiographic progression. (See Table 1A).
are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continued nitroglycerin therapy at 3.1 to 4.4 mg/h (equivalent, in total administered dose of nitrate ions, to 7.8-11.1 mg of isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years 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 bidirectional sequencing when recommended by the mutation test instructions for use.

**6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The overall safety profile of KALYDECO is based on pooled data from the three placebo-controlled trials conducted in 353 patients 6 years of age and older with CF who had a G551D mutation in the CFTR gene (Trials 1 and 2) or were homozygous for the F508del mutation (Trial 3). In addition, the following clinical trials have also been conducted [see Clinical Pharmacology (12) and Clinical Studies (14)]:

- A 24-week, placebo-controlled trial (Trial 5) involving 69 patients between the ages of 6 and 68 years with an R117H mutation in the CFTR gene.
- A 24-week, open-label trial (Trial 6) in 34 patients 2 to less than 6 years of age. Patients eligible for Trial 6 were those with the G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. Of 34 patients enrolled, 32 had the G551D mutation and 2 had the S549N mutation.
- An 8-week, crossover design trial (Trial 7) involving patients between the ages of 12 and 72 years who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO. Of the 335 patients included in the pooled analyses of patients with CF who had either a G551D mutation or were homozygous for the F508del mutation in the CFTR gene, 50% of patients were female and 97% were Caucasian; 221 received KALYDECO, and 132 received placebo from 16 to 48 weeks.

The most common adverse reactions in the 221 patients treated with KALYDECO were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), diarrhea (5%), arthralgia (5%), and bacteria in sputum (5%).

The incidence of adverse reactions below is based on two double-blind, placebo-controlled, 48-week clinical trials (Trials 1 and 2) in a total of 213 patients with CF ages 6 to 53 who have a G551D mutation in the CFTR gene and who were treated with KALYDECO 150 mg orally or placebo twice daily. Table 2 shows adverse reactions occurring in ≥8% of KALYDECO-treated patients with CF who have a G551D mutation in the CFTR gene that also occurred at a higher rate than in the placebo-treated patients in the two double-blind, placebo-controlled trials. (see Table 2)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

KALYDECO is indicated for the treatment CF in pediatric patients age 2-17 years of age who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)].

Clinical trials included the following CF patients:

- ≥18 years old with a R117H mutation in the CFTR gene.
- ≥6 years old with a F508del mutation in the CFTR gene.

**1 INDICATIONS AND USAGE**

**1.1 Clinical Trials Experience**

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**8 USE IN SPECIFIC POPULATIONS**

**8.4 Pediatric Use**

KALYDECO is indicated for the treatment CF in pediatric patients age 2-17 years of age who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)].

Clinical trials included the following CF patients:


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| • 12 to 17 years of age who are heterozygous for the F508del mutation and a second mutation predicted to be responsive to ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)]. (...) |

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

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

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

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

Mutations including F508del that are not responsive to ivacaftor potentiation, based on the in vitro CFTR chloride response threshold, are listed in Figure 1 below the dotted line. (see Figure 1)

Note that splice mutations cannot be studied in this FRT assay and are not included in Figure 1. Evidence of clinical efficacy exists for non-canonical splice mutations 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G and E831X and these are listed in Table 3 below [see also Clinical Studies (14.4)]. The G970R mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor [see Clinical Studies (14.2)].

Ivacaftor also increased chloride transport in cultured human bronchial epithelial (HBE) cells derived from CF patients who carried F508del on one CFTR allele and either G551D or R117H-5T on the second CFTR allele.

Table 3 lists mutations that are responsive to ivacaftor based on 1) a positive clinical response and/or 2) in vitro data in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal). (see Table 3) 12.2 Pharmacodynamics

#### 12.2 Pharmacodynamics Sweat Chloride Evaluation

Changes in sweat chloride (a biomarker) response to KALYDECO were evaluated in seven clinical trials [see Clinical Studies (14)]. In a two-part, randomized, double-blind, placebo-controlled, crossover clinical trial in patients with CF who had a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene (Trial 4), the treatment difference in mean change in sweat chloride from baseline through 8 weeks of treatment was -49 mmol/L (95% CI -57.41). The mean changes in sweat chloride for the mutations for which KALYDECO is indicated ranged from -51 to -8, whereas the range for individual subjects with the G970R mutation was -1 to -11 mmol/L. In an open-label clinical trial in 34 patients ages 2 to less than 6 years administered either 50 mg or 75 mg of ivacaftor twice daily (Trial 6), the mean absolute change from baseline in sweat chloride through 24 weeks of treatment was -45 mmol/L (95% CI -53, -38) [see Use in Specific Populations (8.4)]. In a randomized, double-blind, placebo controlled, 2-period, 3-treatment, 8-week crossover study in patients with CF age 12 years and older who were heterozygous for the F508del mutation and with a second CFTR mutation predicted to be responsive to ivacaftor (Trial 7), the treatment difference in mean change in sweat chloride from study baseline to the average of week 4 and week 8 of treatment for KALYDECO treated patients was -4.5 mmol/L (95% CI -6.7, -2.3).

### 14 CLINICAL STUDIES

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

**Efficacy**

The efficacy of KALYDECO in patients with CF who have a G551D mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving KALYDECO 150 mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study. (...) 14.2 Trial in Patients with a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R Mutation in the CFTR Gene

The efficacy and safety of KALYDECO in patients with CF who had a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, crossover design clinical trial in 39 patients with CF (Trial 4). Patients who completed Part 1 of this trial continued into the 16-week open-label Part 2 of the study. The mutations studied were G178R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. See Clinical Studies (14.1) for efficacy in patients with a G551D mutation. (see Table 5) (...) 14.3 Trial in Patients with CF who have an R117H Mutation in the CFTR Gene

The 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). Fifty-nine of 69 patients completed 24 weeks of treatment. (see Table 6) (...) 14.4 Trial in Patients Homozygous for the F508del Mutation in the CFTR Gene

(...) Eligible patients were heterozygous for the F508del mutation with a second CFTR mutation predicted to be responsive to ivacaftor. (see Table 7) (...) 14.5 Trial in Patients Homozygous for the F508del Mutation in the CFTR Gene

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. (see Table 8) (...)
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### 6 ADVERSE REACTIONS

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

The overall safety profile of ORKAMBI is based on the pooled data from 1108 patients with CF 12 years and older who are homozygous for the F508del mutation in the CFTR gene and who received at least one dose of study drug in 2 double-blind, placebo-controlled, Phase 3 clinical trials, each with 24 weeks of treatment (Trials 1 and 2). Of the 1108 patients, 49% were female and 99% were Caucasian; 369 patients received ORKAMBI every 12 hours and 370 received placebo. Additional safety data in 58 patients with CF ages 12 years and older treated with ORKAMBI who are homozygous for the F508del mutation in the CFTR gene that also occurred at a higher rate than in patients who received placebo in the two double-blind, placebo-controlled trials. (See Table 2)

(…) Table 2 shows adverse reactions occurring in 25% of patients with CF ages 12 years and older treated with ORKAMBI who are homozygous for the F508del mutation in the CFTR gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years [see Clinical Pharmacology (12.3)]. (…)

### 8 USE IN SPECIFIC POPULATIONS

#### 8.4 Pediatric Use
The efficacy of ORKAMBI in children ages 6 through 11 years is extrapolated from efficacy in patients ages 12 years and older homozygous for the F508del mutation in the CFTR gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years [see Clinical Pharmacology (12.3)]. (…)

### 14 CLINICAL STUDIES

#### Confirmatory
The efficacy of ORKAMBI in patients with CF who are homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials (Trials 1 and 2) in 1108 clinically stable patients with CF of whom 369 patients received ORKAMBI twice daily.

#### Table 2
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
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#### 8.4 Pediatric Use
SYMDEKO is indicated for the treatment of CF in pediatric patients ages 12-17 years who are heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor, based on in vitro data and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)].

### 12 CLINICAL PHARMACOLOGY

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

### 14 CLINICAL STUDIES

#### Dose Ranging
Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF homozygous for the F508del mutation (18 years of age and older) with a screening pFEV1≥40. In the study, 34 and 106 patients, respectively, received tezacaftor at once-daily doses of 10 mg, 30 mg, 100 mg, or 150 mg alone or in combination with ivacaftor 150 mg q12h, and 33 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean pFEV1 change from baseline were observed with tezacaftor in combination with ivacaftor. Tezacaftor/ivacaftor in general had a greater mean treatment effect than tezacaftor alone. No additional benefit was observed at tezacaftor doses greater than 100 mg daily.

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<td><strong>Efficacy:</strong></td>
<td>The efficacy of SYMDEKO in patients with CF aged 12 years and older was evaluated in three Phase 3, double-blind, placebo-controlled trials (Trials 1, 2, and 3). Trial 1 was a 24-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were homozygous for the F508del mutation in the CFTR gene. Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in CF patients who were homozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Mutations predicted to be responsive were selected for the study based on the clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro responsiveness to tezacaftor/ivacaftor [see Clinical Studies (14.2)]. Patients were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo. Trial 3 was a 12-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro testing to tezacaftor and/or ivacaftor. (…)</td>
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<td><strong>14.1 Trial in Patients with CF Who Were Homozygous for the F508del Mutation in the CFTR Gene (Trial 1)</strong></td>
<td>Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean ppFEV1 at baseline was 60.0% [range: 27.8% to 96.2%] (see Table 8 and Figure 2) (…)</td>
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<td><strong>14.2 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 2)</strong></td>
<td>Trial 2 evaluated 244 patients with CF aged 12 years and older (mean age 34.8 years). The mean ppFEV1 at baseline was 62.3% [range: 34.6 to 93.5]. Of the 244 patients included in the efficacy analysis, 146 patients had a splice mutation and 98 patients had a missense mutation as the second allele. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (see Table 9). In an analysis of BMI at Week 8, an exploratory endpoint, patients treated with SYMDEKO had a mean improvement of 0.2 kg/m² [95% CI (0.0, 0.3)], 0.1 kg/m² [95% CI (-0.1, 0.5)], and 0.3 kg/m² [95% CI (0.1, 0.5)] versus placebo for the overall, splice, and missense mutation populations of patients, respectively.</td>
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<tr>
<td><strong>14.3 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 3)</strong></td>
<td>Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.1 years) who were heterozygous for the F508del mutation and had a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. CF patients with the F508del mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G&gt;T, 1717-1G&gt;A, 3905insT, 1154insTC, 1811+1.6kbA&gt;G, 2184delA, 405+1G&gt;A, E60X, G85E, L1077P, Q39X, S466X, Y1092X, 1078delT, 1248+1G&gt;A, 2869INSg, 3120+1G&gt;A, 394delTT, 457TAT&gt;G, 11192, 07/20/2018 Oncology IDH1 Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies 211192, 07/20/2018 Oncology IDH1 1 INDICATIONS AND USAGE 1.1 Acute Myeloid Leukemia 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 (14.1)]. 1.2 Pharmacodynamics Multiple doses ofivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies to levels similar to those observed at baseline in healthy subjects. In bone marrow, 2-HG concentrations were reduced by ≥90%. Cardiac Electrophysiology A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state Cmax following a 500 mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 136 patients with relapsed or refractory AML, who received TIBSOVO 500 mg daily [see Warnings and Precautions (5.1)]. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline. 12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Multiple doses ofivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies to levels similar to those observed at baseline in healthy subjects. In bone marrow, 2-HG concentrations were reduced by ≥90%. Cardiac Electrophysiology A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state Cmax following a 500 mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 136 patients with relapsed or refractory AML, who received TIBSOVO 500 mg daily [see Warnings and Precautions (5.1)]. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline. 14 CLINICAL STUDIES 14.1 Acute Myeloid Leukemia The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of 174 adult patients with relapsed or refractory AML with an IDH1 mutation who were assigned to receive a 500 mg daily dose. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTime TM IDH1 Assay, which is the FDA-approved test for selection of patients with AML for treatment with TIBSOVO. In the clinical trial, the most common IDH1 mutation types were R132C and R132H. (See Table 4) (…)</td>
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<tr>
<td>Drug</td>
<td>Therapeutic Area*</td>
<td>Biomarker†</td>
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| 020055, 10/18/2011 | Oncology          | (HER2)     | Clinical Studies  | Combination Therapy (…)
Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6. (…)
Monotherapy HER2-positive patients must also have progressed during or after discontinuation of trastuzumab.
In this study, the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 48% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%. (…)

| 004839, 04/28/2016 | Neurology         | CYP2C19    | Clinical Pharmacology | 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.

| 004046, 10/24/2016 | Gastroenterology  | CYP2C19    | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS
|                   |                   |            |                   | 7.3 Tacrolimus
|                   |                   |            |                   | Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
|                   |                   |            |                   | 12 CLINICAL PHARMACOLOGY
|                   |                   |            |                   | 12.3 Pharmacokinetics
|                   |                   |            |                   | Drug-Drug Interactions
|                   |                   |            |                   | Clobazam
|                   |                   |            |                   | Clobazam 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 clobazam 75 mg alone or concomitantly with PREVACID 30 mg (n=40), for nine days was conducted. (…)

| 002059, 04/06/2017 | Oncology          | ERBB2 (HER2) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
|                   |                   |            |                   | TYKERB® is indicated in combination with:
|                   |                   |            |                   | • 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.
|                   |                   |            |                   | • 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)].
|                   |                   |            |                   | Capecitabine should be taken with food or within 30 minutes after food. If a day’s dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.
|                   |                   |            |                   | Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer

* 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 “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.
‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.
Blue text represents the most recent additions and/or changes since last posted version.
The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be taken once daily (6 tablets administered at all once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)].

2.2 Dose Modification Guidelines

Hepatic Impairment

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

Concomitant Strong CYP3A4 Inducers

The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John’s wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability. (…)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

HER2-Positive Metastatic Breast Cancer

The safety of TYKERB has been evaluated in more than 12,000 patients in clinical trials. (…) Decreases in Left Ventricular Ejection Fraction

Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. (…)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpression (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab. (…) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab. (…) Clinical Studies Describing Limitation of Use: In two randomized trials, TYKERB based chemotherapy regimens have been shown to be less effective than trastuzumab-based chemotherapy regimens. The first randomized, open-label study compared the safety and efficacy of TYKERB in combination with capecitabine relative to trastuzumab in combination with capecitabine breast cancer (N = 540). (…) The second randomized, open-label study compared the safety and efficacy of taxane-based chemotherapy plus TYKERB to taxane-based chemotherapy plus trastuzumab as first-line therapy in women with HER2-positive, metastatic breast cancer (N = 652). (…)

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

The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). Of all patients randomized to treatment, 219 (17%) patients had tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH) ≥2 or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2-negative and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective was to evaluate and compare progression-free survival (PFS) in the HER2-positive population. Progression-free survival was defined as the interval of time between date of randomization and the earlier date of first documented sign of disease progression or death due to any cause. The baseline demographic and disease characteristics were balanced between the two treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty-four percent (84%) of the patients were white. Approximately 50% of the HER2-positive population had prior adjuvant/neoadjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab. In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in progression-free survival (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 7 and Figure 3. (See Table 7 and Figure 3)

1 INDICATIONS AND USAGE

TYKERB is indicated in combination with: (…) luteinizing hormone for whom hormonal therapy is indicated. (…)

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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.
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The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)].

Concomitant Strong CYP3A4 Inducers

The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John’s wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

(…) 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. (…)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

(…) 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 PgR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). (…)

(…) Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 7 and Figure 3. (…)

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 monotheapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among 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.

210961, 11/26/2018

Larotrectinib Oncology NTRK Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies

1 INDICATIONS AND USAGE

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, (…)

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with VITRAKVI based on the presence of a NTRK gene fusion in tumor specimens [see Clinical Studies (14)]. An FDA-approved test for the detection of NTRK gene fusion is not currently available.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

(…) NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Most adults (80%) received VITRAKVI 100 mg orally twice daily and 68% of pediatrics (18 years or younger) received VITRAKVI 100 mg/m2 twice daily up to a maximum dose of 100 mg twice daily. (…)

* Therapeutic areas do not necessarily reflect the CDER review division.
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# Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2018**

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<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
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<td>205834, 02/14/2017</td>
<td>Ledipasvir and Sofosbuvir</td>
<td>Infectious Diseases</td>
<td>JPN3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES The efficacy of VITRAKVI was evaluated in pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials: Study LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). (…) Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH). NTRK gene fusions were inferred in three patients with infantile fibrosarcoma who had a documented ETV6 translocation identified by FISH. (…) The assessment of efficacy was based on the first 55 patients with solid tumors with an NTRK gene fusion enrolled across the three clinical trials. (…) The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (15%), and thyroid cancer (9%). A total of 50 patients had NTRK gene fusions detected by NGS and 5 patients had NTRK gene fusions detected by FISH. Efficacy results are summarized in Tables 4, 5, and 6.</td>
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<td>02/1880, 02/22/2017</td>
<td>Lenalidomide</td>
<td>Hematology</td>
<td>Chromosome 5q</td>
<td>Boxed Warning, Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>BOXED WARNING WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM Hematologic Toxicity (Neutropenia and Thrombocytopenia) REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [see Dosage and Administration (2.3)]. 1 INDICATIONS AND USEAGE 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.</td>
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| Drug | Therapeutic Area | Biomarker | Labeling Sections | Labeling Text*
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<tr>
<td>Lesinurad</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.6%; 53/148) and fatigue (31.1%; 46/148). Table 8 summarizes the adverse events that were reported in ≥ 8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use (…) Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. (…) 14 CLINICAL STUDIES 14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality The efficacy and safety of REVlimid were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1-risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. (…) 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lesinurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, ZURAMPIC exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with CYP2C9 *2/*2 [N=1], and *3/*3 [N=1] genotype) compared to CYP2C9 extensive metabolizers (i.e., CYP2C9 *1/*1 [N=41] genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9 (see Drug Interactions (7.1)).</td>
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| 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. 1.3 First and Second-Line Treatment of Advanced Breast Cancer Femara is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy (see Clinical Studies (14.4, 14.5)). 6 ADVERSE REACTIONS 6.1 Adjuvant Treatment of Early Breast Cancer Bone Study Results of a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = -4.4%) (P=0.0001). (…) Lipid Study In a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen. (…) 14 CLINICAL STUDIES 14.1 Updated Adjuvant Treatment of Early Breast Cancer In a multicenter study enrolling over 8,000 postmenopausal women with resected, receptor-positive early breast cancer, one of the following treatments was randomized in a double-blind manner (See Table 5) (…) 14.2 Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months A double-blind, randomized, placebo-controlled trial of Femara was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease free after 5 years of adjuvant treatment with tamoxifen. (See Table 7) (…) (…) Table 8 shows the study results. Disease-free survival was measured as the time from randomization to the earliest event of loco-regional or distant recurrence of the primary disease or development of contralateral breast cancer or death. DFS by hormone receptor status, nodal status and adjuvant chemotherapy were similar to the overall results. Data were premature for an analysis of survival. (See Table 8) (…) 14.4 First-Line Treatment of Advanced Breast Cancer |

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A randomized, double-blind, multinational trial compared Femara 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIB or loco-regional recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial. (See Table 10) (…) (…) Table 12 shows results in the subgroup of women who had received prior antiestrogen adjuvant therapy. Table 13, results by disease site and Table 14, the results by receptor status. (…) 14.5 Second-Line Treatment of Advanced Breast Cancer Femara was initially studied at doses of 0.1 mg to 5.0 mg daily in six non-comparative Phase II trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least antiestrogen therapy. (See Table 15) (…)

5 WARNINGS AND PRECAUTIONS

5.1 Methemoglobinemia
Prilocaine in Oraqix can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents. Methemoglobinemia has also been reported in a few cases in association with lidocaine treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Oraqix should not be used in those patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents. 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. In severe cases symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrhythmia and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if meth-hb-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level measured with co-oximetry. Normally, metHb levels are <1%, and cyanosis may not be evident until a level of at least 10% is present. The development of methemoglobinemia is generally dose related. The individual maximum level of metHb in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5g Oraqix. (…)

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

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| 209229, 05/10/2018                      | Lofexidine | Anesthesiology | CYP2D6 | Use in Specific Populations | 8 USE IN SPECIFIC POPULATIONS
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 tachycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3%-6% 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
LORBRENA® is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease. (…) |
|                                          |                |                  |      |                   | 6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
(…) 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. (…) |
|                                          |                |                  |      |                   | 14 CLINICAL STUDIES
14.1 ALK-Positive Metastatic NSCLC Previously Treated with an ALK Kinase Inhibitor
The efficacy of LORBRENA was demonstrated in a subgroup of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK kinase inhibitors who were enrolled in a non-randomized, dose-ranging and activity-estimating, multi cohort, multicenter study (Study B7461001; NCT01970865). (…) In addition, for patients with ALK-positive metastatic NSCLC, the extent and type of prior treatment was specified for each individual cohort (See Table 4). (…) |
| 210868, 11/02/2018                      | Lorlatinib (2) | Oncology | ROS1 | Adverse Reactions | 6 ADVERSE REACTIONS
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| 210923, 07/31/2018                      | Lusutrombopag (4) | Hematology | F2 (Prothrombin) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
5.1 Thrombotic/Thromboembolic Complications
(…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 210923, 07/31/2018                      | Lusutrombopag (2) | Hematology | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
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| 210923, 07/31/2018                      | Lusutrombopag (3) | Hematology | PROC | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
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| 210923, 07/31/2018                      | Lusutrombopag (4) | Hematology | PROS1 | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS
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<td>SERPINC1 (Antithrombin III)</td>
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<td>019832, 06/05/1998</td>
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<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>WARNINGS</td>
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<td>Meclizine</td>
<td>Neurology</td>
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<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY</td>
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<td>Mepivacaine (1)</td>
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<td>Warnings</td>
<td>Methemoglobinemia</td>
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<td>012250, 11/02/2018</td>
<td>Mepivacaine (2)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings</td>
<td>Methemoglobinemia</td>
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<td>205919, 02/20/2018</td>
<td>Mercaptopurine (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings and Precautions, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>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 whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)].</td>
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### 12 CLINICAL PHARMACOLOGY

#### 12.5 Pharmacogenomics

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*, 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 [see Dosage and Administration (2.2) and Warnings and Precautions (5.1)].

#### 2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency

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 whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)].

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<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: 1. Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)]. 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>
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<tr>
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<td>Metoclopramide</td>
<td>Gastroenterology</td>
<td>CYB5R</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>
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<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.2 Dosage for Gastroesophageal Reflux Reglan tablets may be administered continuously or intermittently in patients with symptomatic gastroesophageal reflux who fail to respond to conventional therapy: Continuous Dosing: The recommended adult dosage of Reglan is 10 to 15 mg four times daily for 4 to 12 weeks. The treatment duration is determined by endoscopic response. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 60 mg. Table 1 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 1) 2.3 Dosage for Acute and Recurrent Diabetic Gastroparesis The recommended adult dosage for the treatment of acute and recurrent diabetic gastroparesis is 10 mg four times daily for 2 to 8 weeks, depending on symptomatic response. Avoid Reglan treatment for greater than 12 weeks [see Warnings and Precautions (5.1)]. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 40 mg. Table 2 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 2)</td>
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<tbody>
<tr>
<td>019962, 05/06/2014</td>
<td>Metoprolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.9 CYP2D6 Poor Metabolizers Metoprolol is a substrate of CYP2D6. The elimination of metoprolol 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 Rytary [see Clinical Pharmacology (12.3)]. Reduce the Rytary dosage in patients who are poor CYP2D6 metabolizers [see Dosage and Administration (2.2, 2.3)].</td>
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<tr>
<td>207997, 04/28/2017</td>
<td>Midostaurin (1)</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Acute Myeloid Leukemia Rydapt is indicated, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by a FDA approved test [see Dosage and Administration (2.1), Clinical Studies (14.1)]. […] 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the treatment of AML with Rydapt based on the presence of FLT3 mutation positivity [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of FLT3 mutation in AML is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Acute Myeloid Leukemia The safety evaluation of Rydapt (50 mg twice daily with food) in patients with newly diagnosed FLT3 mutated AML is based on a randomized, double-blind, trial of Rydapt (n=345) or placebo (n=335) with chemotherapy [see Clinical Studies (14.1)]. […] Table 2 presents the frequency category of adverse reactions reported in the randomized trial in patients with newly diagnosed FLT3 mutated AML. Adverse reactions are listed according to body system. Within each body system, the adverse reactions are ranked by frequency, with the most frequent reactions first. Table 3 presents the key laboratory abnormalities from the same randomized trial in patients with newly diagnosed FLT3 mutated AML. [see Table 2] […] 14 CLINICAL STUDIES 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 LeukoStrat® CDx FLT3 Mutation Assay, which is an FDA-approved test for selection of patients with AML for Rydapt treatment. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio less than 0.7, and ITD with allelic ratio greater than or equal to 0.7. […] The randomized patients had a median age of 47 years (range, 18-60 years), 44% were male, and 88% had a performance status of 0-1. AML was de novo in 95%. The percentage of patients with FLT3-ITD allelic ratio &lt; 0.7, FLT3-ITD allelic ratio ≥ 0.7, and FLT3-TKD mutations were identical (per randomized FLT3 stratum) on both arms (48%, 30%, and 23%, respectively). […]</td>
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<tr>
<td>207997, 04/28/2017</td>
<td>Midostaurin (2)</td>
<td>Oncology</td>
<td>NPM1</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.1 Acute Myeloid Leukemia Study 1</td>
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(…). 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, (…)

(…).

(…). 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 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 Valenta criteria for ASM and SM-AHN (Table 7). Table 7 shows responses to RYDAPT according to modified Valenta criteria. Confirmed major or partial responses occurred in 46 of 73 patients with a documented KIT D816V mutation, 7 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. (…)

1 INDICATIONS AND USAGE
GALAFOX™ 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)]. (…)

2 DOSAGE AND ADMINISTRATION
• Select adults with confirmed Fabry disease who have an amenable GLA variant for treatment with GALAFOLD [see 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). (…) (…)

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
In Vivo Aminolysis Assay
In an in vitro assay (HEK-293 assay), Human Embryonic Kidney (HEK-293) cell lines were transfected with specific GLA variants (mutations) which produced mutant alpha-Gal A proteins. In the transfected cells, amenableity of the GLA variants was assessed after a 5-day incubation with 10 micromol/L migalastat. A GLA variant was categorized as amenable if the resultant mutant alpha-Gal A activity (measured in the cell lysates) met two criteria: 1) it showed a relative increase of at least 20% compared to the pre-treatment alpha-Gal A activity, and 2) it showed an absolute increase of at least 3% of the wild-type (normal) alpha-Gal A activity. The in vitro assay did not evaluate trafficking of the mutant alpha-Gal A proteins into the lysosome or the dissociation of migalastat from the mutant alpha-Gal A proteins within the lysosome. Also, the in vitro assay did not test whether a GLA variant causes Fabry disease or not.

12.2 Pharmacodynamics
In Study 1, 31 of 50 patients with amenable GLA variants had lyso-Gb3 assessments available after 6 months of treatment. (…)

14 CLINICAL STUDIES
(…).

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism
Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although in vitro studies suggest a role for CYP2D6 and CYP2A4 in the oxidative metabolism of mirabegron, in vivo results indicate that these enzymes play a limited role in the overall elimination. In healthy subjects who are genotypically poor metabolizers of CYP2D6, mean Cmax and AUCt,au were approximately 16% and 17% higher than in extensive metabolizers of
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<tr>
<td>020098, 07/26/2018</td>
<td>Mivacurium</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Warnings, Precautions, Clinical Pharmacology</td>
<td>CYP2D6, respectively. In vitro and ex vivo studies have shown the involvement of butylinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mivacurium, in addition to CYP3A4 and CYP2D6.</td>
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<tr>
<td>020717, 01/15/2015</td>
<td>Modafinil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Interactions with CNS Active Drugs CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine and desipramine) and selective serotonin reuptake inhibitors that are primarily metabolized by CYP2D6. In tricyclic antidepressant patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased. PROVIGIL may cause elevation of the levels of the tricyclics in this subset of patients [see Drug Interactions (7)].</td>
</tr>
<tr>
<td>050791, 10/27/2015</td>
<td>Mycophenolic Acid</td>
<td>Transplantation</td>
<td>HPRT1</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.10 Rare Hereditary Deficiencies Mycophenolic acid is a competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH Inhibitor). Mycophenolic acid should be avoided in patients with rare hereditary deficiency of inosine monophosphate dehydrogenase (HPRT1) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urate nephropathy and renal disease including renal failure.</td>
</tr>
<tr>
<td>014214, 11/28/2012</td>
<td>Nalidixic Acid</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>ADVERSE REACTIONS (…). Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS) (…).</td>
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**Table of Pharmacogenomic Biomarkers in Drug Labeling**

Last Updated: 12/2018

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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</thead>
</table>
| **Nebivolol**                 | Cardiology        | CYP2D6     | Dosage and Administration, Clinical Pharmacology       | 2 DOSAGE AND ADMINISTRATION  
2.2 Subpopulations  
CYP2D6 Polymorphism  
No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers [see Clinical Pharmacology (12.3)]. |
| **Nefazodone**                | Psychiatry        | CYP2D6     | Precautions                                             | PRECAUTIONS  
Cardiovascular-Active Drugs  
Doxogin  
When nefazodone (200 mg BID) and digoxin (0.2 mg QD) were coadministered for 9 days to healthy male volunteers (n = 18) who were phenotyped as CYP2D6 extensive metabolizers, Cmax, Cmin, and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Digoxin had no effects on the pharmacokinetics of nefazodone and its active metabolites. Because of the narrow therapeutic index of digoxin, caution should be exercised when nefazodone and digoxin are coadministered; plasma level monitoring for digoxin is recommended. Propranolol  
The coadministration of nefazodone (200 mg BID) and propranolol (40 mg BID) for 5.5 days to healthy male volunteers (n = 18), including 3 poor and 15 extensive CYP2D6 metabolizers, resulted in 30% and 14% reductions in Cmax and AUC of propranolol, respectively, and a 14% reduction in Cmax for the metabolite, 4-hydroxypropranolol. The kinetics of nefazodone, hydroxynefazodone, and triazole-dione were not affected by coadministration of propranolol. However, Cmax, Cmin, and AUC of m-chlorophenylpiperazine were increased by 23%, 54%, and 26%, respectively. No change in initial dose of either drug is necessary and dose adjustments should be made on the basis of clinical response.  
CYP2D6 isozyme  
A subset (3% to 10%) of the population has reduced activity of the drug-metabolizing enzyme CYP2D6. Such individuals are referred to commonly as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. The pharmacokinetics of nefazodone and its major metabolites are not altered in these “poor metabolizers.” Plasma concentrations of one minor metabolite (mCPP) are increased in this population; the adjustment of nefazodone dosage is not required when administered to “poor metabolizers.” Nefazodone and its metabolites have been shown in vitro to be extremely weak inhibitors of CYP2D6. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme. |
| **Neratinib (1)**             | Oncology          | ERBB2 (HER2) | 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)].  
6 ADVERSE REACTIONS  
ExeNet  
The data described below reflect exposure of NERLYNX as a single agent in ExeNET, 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. (…) |
| **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 ExeNET trial (NCT00877070), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer. |
| **Nilotinib**                 | Oncology          | BCR-ABL1 (Philadelphia chromosome) | 1 INDICATIONS AND USAGE  
1.1 Adult and Pediatric Patients with Newly Diagnosed Ph+ CML-CP |

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Blue text represents the most recent additions and/or changes since last posted version.
Tasigna (nilotinib) is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.

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

Tasigna is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib.

1.3 Pediatric Patients with Resistant or Intolerant Ph+ CML-CP

Tasigna is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy.

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 \( \frac{\text{BCR-ABL}}{\text{ABL}} \leq 0.0032\% \)) 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 \( \frac{\text{BCR-ABL}}{\text{ABL}} \leq 0.01\% \)) 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 \( \frac{\text{BCR-ABL}}{\text{ABL}} \leq 0.0032\% \))
- 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 \( \frac{\text{BCR-ABL}}{\text{ABL}} \leq 0.01\% \)) 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 \( \frac{\text{BCR-ABL}}{\text{ABL}} \leq 0.1\% \)) for 4 consecutive measurements. The patient can then proceed to the original monitoring schedule.

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

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

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

2.7 Dosage Modification for Hepatic Impairment

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

2.8 Dosage Modification with Concomitant Strong CYP3A4 Inhibitors

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

5 WARNINGS AND PRECAUTIONS

9.12 Hemorrhage

In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Tasigna and imatinib, Grade 3 or 4 hemorrhage occurred in 1.1% of patients in the Tasigna 300 mg bid arm, in 1.8% patients in the Tasigna 400 mg bid arm, and 0.4% of patients in the imatinib arm. GI hemorrhage occurred in 2.9% and 5.1% of patients in the Tasigna 300 mg bid and 400 mg bid arms and in 1.4% of patients in the imatinib arm, respectively. Grade 3 or 4 events occurred in 0.7% and 1.4% of patients in the Tasigna 300 mg bid and 400 mg bid arms, respectively, and in no patients in the imatinib arm.

9.17 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 953 mg/day in the Tasigna 300 mg twice daily group. (…)

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

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

Most Frequently Reported Adverse Reactions

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

Laboratory Abnormalities

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

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

The rate of musculoskeletal symptoms decreased in patients who entered the Tasigna treatment reinitiation (NTRI) phase, at 11/88 (12.5%) in the newly diagnosed population and 14/56 (25%) in the population previously treated with imatinib. Other adverse reactions observed in the Tasigna re-treatment phase were similar to those observed 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, 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 that 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=66) [see Clinical Studies (14.5)]. The median time on treatment with Tasigna was 13.8 months (range: 0.7 to 30.9 months). The median actual dose intensity was 435.5 mg/m2/day (range: 149 to 517 mg/m2/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%.

In pediatric patients with Ph+ CML-CP, the most common (greater than 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 patients 2 to 6 years of age.

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</table>
| Use of Tasigna in pediatric patients 1 to less than 18 years of age is supported by evidence from two clinical trials [see Clinical Studies (14.5)]. The 25 patients with newly diagnosed Ph+ CML-CP were in the following age groups: 6 children (age 2 to less than 12 years) and 19 adolescents (age 12 to less than 18 years). The 44 patients with resistant or intolerant Ph+ CML-CP included 18 children (age 2 to less than 12 years) and 26 adolescents (age 12 to less than 18 years). (…)

#### 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 2265 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 (48%), respectively. (…)

##### 12.4 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.

#### 14 CLINICAL STUDIES

##### 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 definition of major cytogenetic response was based on a minimum follow-up of 24 months were enrolled. In this study, about 50% of CML-CP and CML-AP patients were males, over 90% (CML-CP) and 80% (CML-AP) were Caucasian, and approximately 30% were age 65 years or older.

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

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

- The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS)
- No more than two assessments falling between MR4 and MR4.5 (0.0032% IS ≤ BCR-ABL/ABL ≤ 0.01% IS). The median age of patients who entered the TFR phase was 55 years, 49.5% were females, and 21.1% of the patients were ≥65 years of age. BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:
  - Loss of MMR requiring patient to reinstitute Tasigna treatment
  - When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
  - When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

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

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

† Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.

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

Blue text represents the most recent additions and/or changes since last posted version.
Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 12/2018

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>022068, 08/21/2018</td>
<td>Nilotinib (2)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>The ENETStop (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Stop) study (NCT01068905) is an open-label, multicenter, single-arm study, where 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to Tasigna, then switched to Tasigna for at least 2 years), and who achieved MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criterion: • The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during 1 year. (…) Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL &gt; 0.01% IS were considered having a confirmed loss of MR4.0, triggering reinstitution of Tasigna treatment. Patients with loss of MMR in the TFR phase immediately restarted Tasigna treatment without confirmation. All patients who restarted Tasigna therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks. (…) 14.5 Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP The safety and efficacy of Tasigna in pediatric patients with Ph+ CML-CP have been investigated in two studies: Study CAM107A2120 (NCT01077544), an open-label, single-arm, multi-center study that evaluated the pharmacokinetics, safety, and preliminary efficacy of Tasigna in pediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib (n=11), and Study CAM107A2203 (NCT01844765), an open-label, single-arm, multicenter study evaluating the efficacy and safety of Tasigna in pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib (n=33) and newly diagnosed Ph+ CML-CP (n=25). In both studies, patients received Tasigna treatment at a dose of 230 mg/m2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). Data was pooled from a total of 69 pediatric patients (from 2 to less than 18 years of age) with either newly diagnosed Ph+ CML-CP (n=25; 6 children from 2 to less than 12 years and 19 adolescents from 12 to less than 18 years) or imatinib/dasatinib resistant or intolerant Ph+ CML-CP (n=44; 18 children from 2 to less than 12 years and 26 adolescents from 12 to less than 18 years). The median time on treatment with Tasigna was 13.80 months (range: 0.7 to 30.9 months). In patients with resistant or intolerant CML, the major molecular response (MMR; BCR-ABL/ABL ≤ 0.1% IS) rate was 40.9% (18/44; 95% CI: 26.3%, 56.0%) at 12 cycles (28 days per cycle). In patients with newly diagnosed CML, the MMR rate was 60.0% (15/25; 95% CI: 38.7%, 78.9%) at 12 cycles. In patients with resistant or intolerant CML, the cumulative MMR rate was 47.7% (21/44) by cycle 12. In patients with newly diagnosed CML, the cumulative MMR rate was 64.0% (16/25) by cycle 12. Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, the median time to first MMR was 2.8 months (range: 0.0 to 11.3). Among the 17 patients with newly diagnosed CML who achieved MMR, the median time to first MMR was 5.6 months (range: 2.7 to 16.6). Among patients with resistant or intolerant CML, 4.5% of patients achieved BCR-ABL/ABL ≤ 0.0032% IS (MR4.5) by the cut-off date. Among patients with newly diagnosed CML, the percentage of patients who achieved MR4.5 was 28.0%. (See Table 13) (…)</td>
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<td>208447, 03/27/2017</td>
<td>Niraparib</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (…) Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline BRCA mutations (gBRCAm) were assigned to the germline BRCA mutated (gBRCAm) 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>
</tr>
<tr>
<td>009175, 11/04/2013</td>
<td>Nitrofurantoin</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
<td>WARNINGS Hemolytic anemia Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn. ADVERSE REACTIONS Laboratory Adverse Events The following laboratory adverse events have been reported with the use of nitrofurantoin; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see Warnings), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
</table>
| 12554, 11/15/2018                      | Nivolumab (1) | Oncology | BRAF | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Unresectable or Metastatic Melanoma  
• OPDIVO as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma [see Clinical Studies (14.1)].  
• OPDIVO as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma [see Clinical Studies (14.1)]. (…) |

6 ADVERSE REACTIONS  
6.1 Clinical Trials Experience  
Unresectable or Metastatic Melanoma  
Previously Treated Metastatic Melanoma  
(…) In CHECKMATE-037, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (…)  
Previously Untreated Metastatic Melanoma  
CHECKMATE-066  
The safety of OPDIVO was also evaluated in Trial 4, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m² every 3 weeks (n=205) [see Clinical Studies (14.1)]. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. (…) |

14 CLINICAL STUDIES  
14.1 Unresectable or Metastatic Melanoma  
Previously Treated Metastatic Melanoma  
(…) Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. (…)  
(…) Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%). (…)  
(…) There were objective responses in patients with and without BRAF V600 mutation-positive melanoma.  
Previously Untreated Metastatic Melanoma  
CHECKMATE-066  
CHECKMATE-066 was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. (…)  
CHECKMATE-067  
(…) Randomization was stratified by PD-L1 expression (≥ 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). (…)  
(…) Disease characteristics were AJCC Stage IV disease (93%), M1c disease (58%), elevated LDH (36%), history of brain metastases (4%), BRAF V600 mutation-positive melanoma (32%), PD-L1 ≥ 5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (23%). (…)  
14.2 Adjuvant Treatment of Melanoma  
(…) Disease characteristics were AJCC Stage IIIb (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥ 5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%). (…) |

| 12554, 11/15/2018 | Nivolumab (2) | Oncology | CD274 (PD-L1) | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY  
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. |

14 CLINICAL STUDIES  
14.1 Unresectable or Metastatic Melanoma  
Previously Treated Metastatic Melanoma  
CHECKMATE-066  
(…) Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). (…)  
(…) Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%); Reference ID: 419838 (11%), elevated LDH level (37%); PD-L1 greater than or equal to 5% tumor cell membrane expression (35%), and history of brain metastases (4%). (…)  
CHECKMATE-067  
(…) Randomization was stratified by PD-L1 expression (≥ 5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b versus M1c). (…) |

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</thead>
</table>
| (…). A total of 945 patients were randomized, 314 patients to the OPDIVO plus ipilimumab arm, 316 to the OPDIVO arm, and 315 to the ipilimumab arm. The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (65%); M1c disease (58%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%). (…)

(…). Figures 3 and 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx assay. Tumor samples were available for retrospective assessment for 97% of the study population; PD-L1 expression status was ascertained for 89% of the study population while in 6% of patients, melanin precluded evaluation of PD-L1 expression status. PD-L1 expression status was unknown for 5% of the study population due to consent withdrawal or missing samples. (see Figures 3 and 4)

The data presented in the figure below summarize the results of exploratory analyses comparing the two OPDIVO-containing arms in subgroups defined by PD-L1 tumor expression. (see Figure 5) (…)

14.2 Adjuvant Treatment of Melanoma CHECKMATE-238

(…). Randomization was stratified by PD-L1 status (positive [based on 5% level] vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage IIIb/C vs Stage IV M1a-M1b vs Stage IV M1c). (…)

(…). Disease characteristics were AJCC Stage IIIb (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%). (…)

14.3 Metastatic Non-Small Cell Lung Cancer (NSCLC)

Second-line Treatment of Metastatic Squamous NSCLC CHECKMATE-017

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

(…). Archival tumor specimens were retrospectively evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (208/455) PD-L1 negative, defined as <1% of tumor cells expressing PD-L1, and 54% (246/455) PD-L1 positive NSCLC, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive NSCLC subgroup. (…)

Second-line Treatment of Metastatic Non-Squamous NSCLC CHECKMATE-057

(…). The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression. (…)

(…). Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (208/455) PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% (246/455) PD-L1 positive NSCLC, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive NSCLC subgroup. (…)

14.4 Small Cell Lung Cancer

CHECKMATE-032 (NCT01503934) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic solid tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinum-based chemotherapy to receive treatment with OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. (…)

14.5 Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after 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 28) (…)

Previously Untreated Renal Cell Carcinoma

CHECKMATE-214 (NCT02531749) 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) (…)

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 of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. (…)

14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

CHECKMATE-141

(…). 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 nonquantifiable results. Among the 250 patients with quantifiable results, 43% (111/250) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (139/250) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. (…)

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tumor cells expressing PD-L1, and 57% (149/260) had PDL1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified 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 SCCHN 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 pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients, were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 27. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%). (see Table 33)

1 INDICATIONS AND USAGE
1.8 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

• OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.9)].

• OPDIVO, in combination with ipilimumab, is indicated for the treatment of adults and pediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.9)].

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION
2.9 Recommended Dosage for MSI-H/dMMR CRC

Single Agent

The recommended dose of OPDIVO as a single agent is 240 mg every 2 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

With ipilimumab

The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for 4 doses [see Clinical Studies (14.9)]. After completing 4 doses of the combination, administer OPDIVO 240 mg as a single agent every 2 weeks as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

Review the Prescribing Information for ipilimumab prior to initiation.

6 ADVERSE REACTIONS

Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer

The safety of OPDIVO administered as a single agent in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label study. (See Tables 20 and 21) (…)
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<td>018013, 07/28/2014</td>
<td>Nortriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS. Drugs Metabolized by P450 2D6. The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called &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>
</tr>
<tr>
<td>289931, 10/10/2018</td>
<td>Nusinersen</td>
<td>Neurology</td>
<td>SMN2</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY. 12.2 Pharmacodynamics. Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants.</td>
</tr>
<tr>
<td>125488, 02/26/2016</td>
<td>Obinutuzumab</td>
<td>Oncology</td>
<td>MS4A1 (CD20 antigen)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES. 14.1 Chronic Lymphocytic Leukemia. GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (Study 1) in 781 patients with previously untreated CD20+ chronic lymphocytic leukemia requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) ≤ 70 mL/min. (...)</td>
</tr>
<tr>
<td>208558, 12/19/2018</td>
<td>Olaparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Events, Clinical Studies</td>
<td>1 INDICATIONS AND USE. 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 (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)].</td>
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<td>Advanced gBRCA-mutated Ovarian Cancer</td>
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<td>Continue treatment until disease progression or unacceptable toxicity.</td>
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<td>Germline BRCA-mutated HER2-negative Metastatic Breast Cancer</td>
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<td>Continue treatment until disease progression or unacceptable toxicity.</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia</td>
<td>Overall, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) in patients treated with Lynparza monotherapy in clinical trials, including long-term follow up, was &lt;1.5% (%26/2255) 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>
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<td>6 ADVERSE REACTIONS</td>
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<td>First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer</td>
<td>SOLO-1</td>
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<td>Maintenance Treatment of Recurrent Ovarian Cancer</td>
<td>SOLO-2</td>
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<td>Treatment of Advanced gBRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy</td>
<td>Pooled data</td>
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<td>Treatment of gBRCA-mutated HER2-negative Metastatic Breast Cancer</td>
<td>OlympiAD</td>
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<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer</td>
<td>SOLO-1</td>
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<td>Study 19</td>
<td>A retrospective analysis for germline BRCA mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious gBRCA mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo.</td>
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<td>14.2 Maintenance Treatment of Recurrent Ovarian Cancer</td>
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<td></td>
<td>14.3 Advanced gBRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy</td>
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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  
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)].  

2 DOSAGE AND ADMINISTRATION  
2.1 Patient Selection  
gBRCAm HER2-negative Metastatic Breast Cancer  
Select patients for the treatment of HER2-negative metastatic breast cancer with Lynparza based on the presence of deleterious or suspected deleterious gBRCA-mutation [see Indications and Usage (1.4) and Clinical Studies (14.3)].  

2.2 Recommended Dosing  
Germline BRCA-mutated HER2-negative Metastatic Breast Cancer  
Continue treatment until disease progression or unacceptable toxicity.  

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  
OlympiAD  
OlympiAD (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 (capcitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. (…)  

| 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, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)].  

14 CLINICAL STUDIES  
14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer  
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|----------------------------------------|------|----------------|-----------|-------------------|----------------
| 761038, 10/19/2016                    | Olaratumab | Oncology | PDGFRA | Clinical Studies | 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 PDGFR-α expression by an investigational use assay. Patients were randomized (1:1) to receive LARTRUVO in combination with docorubicin or doxorubicin as a single agent. PDGFR-α expression (positive versus negative) number of previous lines of treatment (0 versus 1 or more), histological tumor type (kaposimo sarcoma versus synovial sarcoma versus all others), and ECOG PS (0 or 1 versus 2) were used to allocate patients in the randomization. (...) 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. (...)|
| 203855, 05/01/2014                    | Omacetaxine | Oncology | BCR-ABL1 (Philadelphia chromosome) | 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) |
| 207931, 02/14/2017                    | Ombitasvir, Paritaprevir, and Ritonavir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14 CLINICAL STUDIES | (…) HCV GT4-infected subjects had a median age of 51 years (range: 19 to 70); 64% were treatment-naïve, 17% were prior pegIFN/RBV null responders; 7% were prior pegIFN/RBV partial responders, 13% were prior pegIFN/RBV relapsers; 65% were male; 9% were Black, 14% had a body mass index at least 30 kg/m²; 70% had baseline HCV RNA levels at least 800,000 IU/mL; 79% had IL28B (rs12979860) non-CC genotype; 7% had bridging fibrosis (F3). (...) |
| 020007, 09/18/2014                    | Omeprazole | Gastroenterology | CYP2C19 | Drug Interactions, Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY | CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are extensive metabolizers and those carrying two loss-of-function alleles are poor metabolizers. In extensive metabolizers, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient’s metabolism status: poor metabolizers > intermediate metabolizers > extensive metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers. In a pharmacokinetic study of single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four-fold of that in Caucasians [see Dosage and Administration (2.1), Use in Specific Populations (8.7)]. |
| 020007, 09/18/2014                    | Ondansetron | Gastroenterology | CYP2D6 | Clinical Pharmacology | 12 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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</table>
| 208065, 08/28/2018                      | Osimertinib | Oncology | EGFR | Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies | **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)].

<table>
<thead>
<tr>
<th>2 DOSAGE AND ADMINISTRATION</th>
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</table>

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)]. Testing for presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

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<th>6 ADVERSE REACTIONS</th>
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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 (9)]. 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.

**Precedently 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. (…)

**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 previously treated EGFR T790M mutation-positive NSCLC who had progressive disease following first line EGFR TKI treatment. (…)

**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 institutional laboratory. (…)

Randomization was stratified by EGFR 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. (…)

With regard to EGFR tumor testing, 63% were exon 19 deletion and 37% were exon 21 L858R. Patients <1% had a comorbidity of non-T790M mutation. EGFR mutation status was confirmed centrally using the cobas EGFR Mutation Test in 90% of patients. (see Table 6 and Figure 1) (…)

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. (…)

**203505, 01/25/2019**

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<td><strong>12 CLINICAL PHARMACOLOGY</strong></td>
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12.3 Pharmacokinetics

**Drug Interactions**

Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug

Ospemifene 60 mg was given after a light breakfast (two slices of bread with ham and cheese and juice) once daily for 12 days in sixteen postmenopausal women who were determined to be rapid metabolizers of CYP2C9 (CYP2C9*1/*1 or CYP2C9*1/*2). On Day 8, a single dose of warfarin 10 mg and vitamin K 10 mg were administered one hour after a light breakfast. The geometric mean ratio (90% CI) for S-warfarin with and without ospemifene for Cmax and AUC0-inf were 0.97 (0.92-1.02) and 0.96 (0.91-1.02), respectively. Multiple doses of ospemifene did not significantly affect the pharmacokinetics of a single dose of warfarin. No study was conducted with multiple doses of warfarin.

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<td>Ospemifene (2)</td>
<td>Gynecology</td>
<td>CYP2B6</td>
<td>12.3 Pharmacokinetics</td>
<td>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 AUC0-inf were 0.82 (0.75-0.91) and 0.81 (0.77-0.86), respectively. The geometric mean ratio (90% CI) for hydroxybupropion, an active metabolite formed via CYP2B6, with and without ospemifene for Cmax and AUC0-inf were 1.16 (1.09-1.24) and 0.98 (0.92-1.04), respectively.</td>
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<tr>
<td>202810, 12/04/2015</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 Oxelirex 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 Oxelirex 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 Oxelirex 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 Oxelirex XR. The use of Oxelirex 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 Oxelirex XR users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B</em>1502 status. The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been well characterized.</td>
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<td>208032, 11/02/2018</td>
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<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)</td>
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<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.1 Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue KOVANAZE and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.</td>
</tr>
<tr>
<td>207103, 02/06/2018</td>
<td>Palbociclib (1)</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage</td>
<td>1 INDICATIONS AND USAGE IBRANCE is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or fulvestrant in women with disease progression following endocrine therapy.</td>
</tr>
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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
</tr>
</thead>
</table>
| 207/103, 02/06/2018                   | Palbociclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
IBRANCE is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:
• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
• fulvestrant in women 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 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.

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Palbociclib is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palbociclib and 6-S-hydroxy-palbociclib. These metabolites each have less than 1% of the 5-HT3 receptor antagonist activity of palbociclib. In vitro metabolism studies have suggested that...

201372, 09/18/2014
Palonosetron | Gastroenterology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that...

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<td>125147, 06/29/2017</td>
<td>Panitumumab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of panitumumab. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.</td>
</tr>
<tr>
<td>125147, 06/29/2017</td>
<td>Panitumumab (2)</td>
<td>Oncology</td>
<td>RAS</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USE: 1.1 Metastatic Colorectal Cancer: Vectibix is indicated for the treatment of patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) [see Dosage and Administration (2.1); • As first-line therapy in combination with FOLFOX [see Clinical Studies (14.2)]; • As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy [see Clinical Studies (14.1)]; 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)].</td>
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</table>
| **RAS mCRC** is similar with that seen in patients with wild-type KRAS mCRC. | Vectibix in Combination with FOLFOX Chemotherapy | The most commonly reported adverse reactions (≥20%) in patients with wild-type KRAS mCRC receiving Vectibix (6 mg/kg every 2 weeks) and FOLFOX therapy (N = 322) in Study 20050203 were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypogammaglobulinemia, hypokalemia, rash, acneiform dermatitis, prunus, 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, acneform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypokalemia, occurred in a patient who received Vectibix. (See Table 2) (…)

### 14 CLINICAL STUDIES

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

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

(…) The study results were analyzed in the wild-type KRAS subgroup where KRAS status was retrospectively determined using archived paraffin-embedded tumor tissue. KRAS mutation status was determined in 427 patients (92%) of these, 343 (77%) had no detectable KRAS mutations in either codons 12 or 13. The hazard ratio for PFS in patients with wild-type KRAS mCRC was 0.45 (95% CI: 0.34-0.59) favoring the panitumumab arm. The response rate was 17% for the panitumumab arm and 0% for BSC. There were no differences in OS; 77% of patients in the BSC arm received panitumumab at the time of disease progression. Study 20080763 (NCT01600137)

Study 20080763 was an open-label, multicenter, multinational, randomized (1:1) clinical trial, stratified by region (North America, Western Europe, and Australia versus rest of the world) and ECOG 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 or 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 (5 mg/kg intravenously every 14 days) plus BSC or BSC alone. Patients received Vectibix and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. Study 20100007 (NCT01412987)

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 the 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 or 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 (5 mg/kg intravenously every 14 days) plus BSC or BSC alone. Patients received Vectibix and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. Study 20100007 (NCT01412987)

Exploratory Analysis of OS

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

In the wild-type RAS subgroup, 65% of patients were men and 91% were White, 2% Black, and 5% Hispanic or Latino. Sixty-five percent of patients had colon cancer and 35% had rectal cancer. ECOG performance was 0 in 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) (…) (…)

14.2 First-line in Combination with FOLFOX Chemotherapy

(…) The prespecified major efficacy measure was PFS in patients (n = 656) with wild-type KRAS mCRC as assessed by a blinded independent central review of imaging. Other key efficacy measures included OS and ORR. In Study 20050203, in the wild-type KRAS subgroup (n = 656), 64% of patients were men, 92% White, 2% Black, and 4% Hispanic or Latino. Sixty-six percent of patients had colon cancer and 34% had rectal cancer. ECOG performance was 0 in 56% of patients, 1 in 38% of patients, and 2 in 6% of patients. Median age was 61.5 years. The efficacy results in Study 20050203 in patients with wild-type KRAS mCRC are presented in Table 5 below. (See Table 5) (…) (…)

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 14 and 16) of KRAS or NRAS. In Study 20050203, among patients with RAS-mutant tumors, the median PFS was 7.3 months (95% CI: 6.3, 7.9) among 272 patients receiving Vectibix plus FOLFOX and 8.7 months (95% CI: 7.6, 9.4) among patients who received FOLFOX alone (HR = 1.31, 95% CI: 1.07, 1.60). The median OS was 15.6 months (95% CI: 14.6, 16.4) vs 20.7 months (95% CI: 18.7, 22.6) among patients receiving FOLFOX alone (HR = 1.50, 95% CI: 1.25, 1.80). (See Table 5) (…)

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<tbody>
<tr>
<td>020987, 12/20/2017</td>
<td>Pantoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although sera half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Doses higher than 40 mg/day have not been studied in hepatically impaired patients.</td>
</tr>
<tr>
<td>125511, 06/10/2016</td>
<td>Parathyroid Hormone</td>
<td>Inborn Errors of Metabolism</td>
<td>CASR</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Limitations of Use: • Because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone [see Warnings and Precautions (5.1)]. • NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations. • NATPARA was not studied in patients with acute post-surgical hypoparathyroidism.</td>
</tr>
<tr>
<td>021299, 01/04/2017</td>
<td>Paroxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>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 and in atomoxetine Cmax values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.</td>
</tr>
<tr>
<td>210822, 08/10/2018</td>
<td>Patisiran</td>
<td>Neurology</td>
<td>TTR</td>
<td>Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>6 ADVERSE REACTIONS... At baseline, 48% of patients were in Stage 1 of the disease and 53% were in Stage 2. Forty-three percent of patients had Val30Met mutations in the transthyretin gene; the remaining patients had 38 other point mutations. Sixty-two percent of ONPATTRO-treated patients had non-Val30Met mutations, compared to 48% of the placebo-treated patients.</td>
</tr>
<tr>
<td>022465, 05/31/2017</td>
<td>Pazopanib (1)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics Pazopanib can increase serum total bilirubin levels [see Warnings and Precautions (5.1)]. In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. A pooled pharmacogenetic analysis of 238 Caucasian patients evaluated the TA-repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during pazopanib treatment. In this analysis, the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic susceptibility to Gilbert’s syndrome) was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)5/(TA)5 genotypes.</td>
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<tr>
<td>022465, 05/31/2017</td>
<td>Pazopanib (2)</td>
<td>Oncology</td>
<td>HLA-B</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics (...). In a pooled pharmacogenetic analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, ALT &gt; 3 X ULN (NCI CTC Grade 2) occurred in 32% (42/133) of HLA-B<em>57:01 allele carriers and in 19% (39/2101) of non-carriers and ALT &gt; 5 X ULN (NCI CTC Grade 3) occurred in 19% (25/133) of HLA-B</em>57:01 allele carriers and in 10% (213/2101) of non-carriers. In this dataset, 6% (133/2234) of the patients carried the HLA-B*57:01 allele. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype [see Warnings and Precautions (5.1)].</td>
</tr>
<tr>
<td>103949, 09/16/2015</td>
<td>Peginterferon Alfa-2b</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics A retrospective genome-wide association analysis of 1,2 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 rs12979860 genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to IL28B genotype was consistent across various racial/ethnic groups (see Table 14). Other variants near the IL28B gene (e.g., rs8099917 and rs103142) have been identified; however, they have not been shown to independently influence SVR rates during treatment with pegylated interferon alpha therapies combined with ribavirin. (See Table 14)</td>
</tr>
<tr>
<td>125293, 09/09/2016</td>
<td>Pegloticase</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Boxed Warning: WARNING: ANAPHYLAXIS AND INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA • (…) Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency (4.5.3).</td>
<td></td>
</tr>
<tr>
<td>125514, 12/28/2018</td>
<td>Pembrolizumab (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience</td>
<td>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>(2)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Studies</td>
</tr>
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1. INDICATIONS AND USAGE
1.2 Non-Small Cell Lung Cancer
KEYTRUDA, in combination with pembrolizumab 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 nab-paclitaxel, 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 metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥50%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations.

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.

1.5 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 (Combined Positive Score (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 (14.6)]. 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 [see Clinical Studies (14.6)].

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.

1.9 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 (14.9)]. 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, 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:
• metastatic NSCLC [see Clinical Studies (14.2)]
• metastatic urothelial carcinoma [see Clinical Studies (14.6)]
• metastatic gastric cancer [see Clinical Studies (14.8)]. 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 (14.9)].

Information on FDA-approved tests for the detection of PD-L1 expression for these indications is available at: http://www.fda.gov/CompanionDiagnostics

14 CLINICAL STUDIES
14.1 Melanoma
Ipilimumab-Naive Melanoma
(….) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. (….) The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator’s choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was two or more prior therapies for advanced or metastatic disease. (….)

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 BRAF V600 mutation 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, 13% (46%) were previously treated with a BRAF inhibitor. (….)

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<tr>
<td><strong>14.2 Non-Small Cell Lung Cancer</strong></td>
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<tr>
<td>First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy</td>
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<td>The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGRA or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cispain vs. carboplatin), and tumor PD-L1 status (TPS &lt;1% [negative] vs. TPS ≥1%). (See Table 21) (…)</td>
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<tr>
<td>First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy</td>
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<td>The efficacy of KEYTRUDA in combination with carboplatin and investigator’s choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS &lt;1% [negative] vs. TPS ≥1%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). (…)</td>
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<td><strong>14.6 Urothelial Carcinoma</strong></td>
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<tr>
<td>Cisplatin Ineligible Patients with Urothelial Carcinoma</td>
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<td>(…) Among the 310 patients, 30% (n = 93) 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 87% White. (See Table 28) (…)</td>
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<td><strong>125514, 12/28/2018</strong></td>
<td>Pembrolizumab (3)</td>
<td>Oncology</td>
<td>Microsatellite Instability, Indications and Usage, Dosage and Administration</td>
<td>1 INDICATIONS AND USAGE</td>
<td>1.7 Microsatellite Instability-High Cancer</td>
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</table>
| 010775, 05/10/2002                     | Perphenazine | Psychiatry | CYP2D6 | Precautions, Clinical Pharmacology | PRECAUTIONS Drug Interactions Metabolism of a number of medications, including antipsychotics, antidepressants, beta-blockers, and antihistaminics, occurs through the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called “poor” metabolizers. Among other populations the prevalence is not known. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. In one study of 45 elderly patients suffering from dementia treated with perphenazine, the 5 patients who were prospectively identified as poor P450 2D6 metabolizers had reported significantly greater side effects during the first 10 days of treatment than the 40 extensive metabolizers, following which the groups tended to converge. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events. (…)

12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics (…) The pharmacokinetics of perphenazine covary with the hydroxylation of debrisoquine which is mediated by cytochrome P450 2D6 (CYP 2D6) and thus is subject to genetic polymorphism—i.e., 7%-10% of Caucasians and a low percentage of Asians have little or no activity and are called “poor metabolizers.” Poor metabolizers of CYP 2D6 will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or “extensive” metabolizers. (…) |
| 125409, 03/22/2016                     | Pertuzumab (1) | Oncology | ERBB2 (HER2) | Indications and Usage, 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 Neoadjuvant Treatment of Breast Cancer PERJETA is indicated for use in combination with trastuzumab and docetaxel 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. |

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<td>This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival [see Clinical Studies (14.2) and Dosage and Administration (2.1)]. (…)</td>
</tr>
</tbody>
</table>

#### 5 WARNINGS AND PRECAUTIONS

5.1 Left Ventricular Dysfunction
Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. In Study 1, for patients with MBC, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel [see Clinical Studies (14.1)]. (…)

5.2 Embryo-Fetal Toxicity
Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. (…)

5.5 HER2 Testing
Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy because these are the only patients studied and for whom benefit has been shown [see Indications and Usage (1) and Clinical Studies (14)]. Patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 in the clinical studies. Only limited data were available for patients whose breast cancer was positive by FISH, but did not demonstrate protein overexpression by IHC. Assessment of HER2 status should be performed by laboratories using FDA-approved tests with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
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. (…)

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of PERJETA in pregnant women. However, in post-marketing reports, use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. (…)

#### 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 on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in Study 1. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.

#### 14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer
Study 1 was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment. (…)

Study 2 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 PERJETA plus docetaxel. Randomization was stratified by breast cancer type (operative, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. (…)

Study 3

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<td>Perjeta</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>(...) An additional phase 2 neoadjuvant study 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. (…)</td>
</tr>
<tr>
<td>010151, 06/16/2016</td>
<td>Phenytoin (1)</td>
<td>Neurology</td>
<td>CYP2C9</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY (…) 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 or CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. (…)</td>
</tr>
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<td>010151, 06/16/2016</td>
<td>Phenytoin (2)</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY (…) 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 or 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>WARNINGS Serious Dermatologic Reactions Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. Dilantin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (see DRESS/Multorgan hypersensitivity below). Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B<em>1502, an inherited allelic variant of the HLA-B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B</em>1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B<em>1502. The use of HLA-B</em>1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.</td>
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<tr>
<td>017473, 09/27/2011</td>
<td>Pimozide</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Precautions</td>
<td>DOSAGE AND ADMINISTRATION Children Reliable dose response data for the effects of ORAP (pimozide) on tic manifestation in Tourette’s Disorder patients below the age of twelve are not available. Treatment should be initiated at a dose of 0.05 mg/kg preferably taken once at bedtime. The dose may be increased every third day to a maximum of 0.2 mg/kg not to exceed 10 mg/day.</td>
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| 018147, 05/09/2016                    | Piroxicam | Rheumatology | CYP2C9 | Clinical Pharmacology | At doses above 0.05 mg/kg/day, CYP 2D6 genotyping should be performed. In poor CYP 2D6 metabolizers, ORAP doses should not exceed 0.05 mg/kg/day, and doses should not be increased earlier than 14 days (see Precautions – Pharmacogenomics).
In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg/day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended. At doses above 4 mg/day, CYP 2D6 genotyping should be performed. In poor CYP 2D6 metabolizers, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days (see Precautions – Pharmacogenomics).
PRECAUTIONS Pharmacogenomics
Individuals with genetic variations resulting in poor CYP 2D6 metabolism (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than extensive CYP 2D6 metabolizers. The concentrations observed in poor CYP 2D6 metabolizers are similar to those seen with strong CYP 2D6 inhibitors such as paroxetine. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP 2D6 metabolizers because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically poor CYP 2D6 metabolizers (see Dosage and Administration).

PRECAUTIONS Pharmacogenomics
Individuals with genetic polymorphisms resulting in poor CYP2C9 metabolism (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than extensive CYP2C9 metabolizers. The concentrations observed in poor CYP2C9 metabolizers are similar to those seen with strong CYP2C9 inhibitors such as paroxetine. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP2C9 metabolizers because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically poor CYP2C9 metabolizers (see Dosage and Administration).

PONATINIB [BCR-ABL1 (Philadelphia chromosome)] Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INICATIONS AND USAGE
Iclusig (ponatinib) is a kinase inhibitor indicated for:• Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
• Treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
Limitations of use
Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML [see Warnings and Precautions (5.7)].

5 WARNINGS AND PRECAUTIONS
5.2 Venous Thromboembolism
Venous thromboembolic events occurred in 6% (25/449) of Iclusig-treated patients, including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients).
In the phase 2 trial, the incidence of venous thromboembolism was 9% (3/32) in patients with Ph+ ALL, 10% (6/62) in patients with blast phase (BP) CML, 4% (3/85) in patients with AP-CML, and 5% (13/270) in patients with CP-CML. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism [see Dosage and Administration (2.3)].

5.4 Hepatotoxicity
Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts. (…)

5.10 Hemorrhage
Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Iclusig in the phase 2 trial, with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% (4/449) and 4/449, respectively. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia [see Warnings and Precautions (5.13)]. Interrupt Iclusig for serious or severe hemorrhage and evaluate [see Dosage and Administration (2.3)].

5.13 Myelosuppression
Myelosuppression was reported as an adverse reaction in 59% (266/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Iclusig. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (…)

5.14 Tumor Lysis Syndrome

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<td>Cardiology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>Two patients (&lt;1%) treated with Iclusig developed serious tumor lysis syndrome. One case occurred in a patient with advanced AP-CML and one case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig.</td>
</tr>
</tbody>
</table>

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Previously Treated CML or Ph+ ALL

The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. (…) At the time of analysis (48 months of follow-up), 133 patients (30%) were ongoing (110 CP-CML; 20 AP-CML; 3 BP-CML; 0 Ph+ ALL), and the median duration of treatment with Iclusig was 32.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML, and 2.7 months in patients with Ph+ ALL. (…) The rates of treatment-emergent adverse reactions resulting in discontinuation were 19% in CP-CML, 12% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse reactions that led to treatment discontinuation was thrombocytopenia (4%). (See Table 5) (…) Laboratory Abnormalities (…) Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (See Table 7) (…)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

14 CLINICAL STUDIES

The safety and efficacy of Iclusig in patients with CML and Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter trial. Efficacy results described below should be interpreted within the context of updated safety information [see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1, 5.2)]. All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; blast phase CML [Ph+ ALL]; Philadelphia-positive acute lymphoblastic leukemia [BP-CML/Ph+ ALL]); resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation. Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ ALL. The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). The trial enrolled 449 patients, of which 444 were eligible for efficacy analysis: 267 patients with CP-CML (R/I Cohort: n=203, T315I: n=64), 83 patients with AP-CML, 82 patients with BP-CML, and 32 patients with Ph+ ALL. Five patients were not eligible for efficacy analysis due to lack of confirmation of T315I mutation status, and these patients had not received prior dasabigitib or nilotinib. (See Table 11) (…) At the time of analysis, there were 133 patients ongoing (110 patients with CP-CML; 20 patients with AP-CML; 3 patients with BP-CML; 0 patients with Ph+ ALL), and the median duration of Iclusig treatment was 32.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML and 2.7 months in patients with Ph+ ALL. (See Table 12 and 13) (…) The median time to MMR in patients with AP-CML, BP-CML, and Ph+ ALL was 0.7 months (range: 0.4 to 5.8 months), 1.0 month (range: 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months), respectively. The median duration of MMR for patients with AP-CML, BP-CML, and Ph+ ALL was 12.9 months (range: 1.2 to 52+ months), 6.0 months (range: 1.8 to 47.4+ months), and 3.2 months (range: 1.8 to 12.8+ months), respectively.

022307, 07/12/2016

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.

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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.

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.

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.

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.

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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.

Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings). Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support to manage hemolytic risk should be available. Primaquine should not be prescribed for patients with severe G6PD deficiency (see Contraindications).

CONTRAINDICATIONS

Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings).

WARNINGS

Hemolytic anemia and G6PD deficiency

Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Primaquine should not be prescribed for patients with severe G6PD deficiency (see Contraindications).

In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available.
### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area†</th>
<th>Biomarker‡</th>
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<th>Labeling Text‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>008316, 06/22/2017</td>
<td>Primaquine (2)</td>
<td>Infectious Diseases</td>
<td>CYB5R</td>
<td>Precautions, Adverse Reactions</td>
<td>When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. Discontinue the use of primaquine phosphate promptly if signs suggestive of hemolytic anemia occur (darkening of the urine, marked fall of hemoglobin or erythrocytic count). Hemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia, and Oceania. People from these regions have a greater tendency to develop hemolytic anemia (due to a congenital deficiency of erythrocytic G6PD) while receiving primaquine and related drugs. Use in Pregnancy: Safe usage of this preparation in pregnancy has not been established. Primaquine is contraindicated in pregnant women. Even if a pregnant woman is G6PD normal, the fetus may not be (see Contraindications).</td>
</tr>
<tr>
<td>007898</td>
<td>Probencid</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Adverse Reactions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<tr>
<td>020545</td>
<td>Procainamide</td>
<td>Cardiology</td>
<td>Non-specific (NAT)</td>
<td>Adverse Reactions, Clinical Pharmacology</td>
<td>Labeling not electronically available on Drugs@FDA</td>
</tr>
<tr>
<td>021416, 02/14/2013</td>
<td>Propafenone</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION: The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor [see Warnings and Precautions (5.4) and Drug Interactions (7.1)]. 5 WARNINGS AND PRECAUTIONS 5.4 Drug Interactions: Simultaneous Use with Inhibitors of Cytochrome P450 Isoenzymes 2D6 and 3A4: Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6 activity and to a somewhat lesser extent in other demographic groups. Drugs that inhibit these CYP pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP2D6; ketoconazole, erythromycin, saquinavir, and grapefruit juice for CYP3A4; and amiodarone and tobacco smoke for CYP1A2) can be expected to cause increased plasma levels of propafenone. Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>021438, 11/19/2013</td>
<td>Propranolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.1 CYP2D6 and CYP3A4 Inhibitors Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline) and CYP3A4 (such as ketoconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be expected to cause increased plasma levels of propafenone. The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with administration of propafenone may increase the risk of adverse reactions, including proarrhythmia. Therefore, simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided (see Warnings and Precautions (5.4) and Dosage and Administration (2)).</td>
</tr>
<tr>
<td>073644, 07/17/2014</td>
<td>Protriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS Drugs Metabolized by Cytochrome P450 2D6 The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA). (…)</td>
</tr>
<tr>
<td>089033, 02/02/2010</td>
<td>Quinidine</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>PRECAUTIONS (…) Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient “poor metabolizers” from the majority-phenotype “extensive metabolizers”. When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the case of prodrugs whose actions are actually mediated by P450IID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers. Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6. (…)</td>
</tr>
<tr>
<td>021799, 07/02/2014</td>
<td>Quinine Sulfate (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS QUALAQUIN is contraindicated in patients with the following: • Glucose-6-phosphate dehydrogenase (G6PD) deficiency. • Hemolysis can occur in patients with G6PD deficiency receiving quinine. (…)</td>
</tr>
<tr>
<td>021799, 07/02/2014</td>
<td>Quinine Sulfate (2)</td>
<td>Infectious Diseases</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS 7.2 Effects of Quinine on the Pharmacokinetics of Other Drugs</td>
</tr>
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<tbody>
<tr>
<td>020973, 04/04/2016</td>
<td>Rabeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>Desipramine (CYP2D6 substrate) Quinine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. [...]</td>
</tr>
<tr>
<td>020815, 06/27/2018</td>
<td>Raloxifene</td>
<td>Oncology</td>
<td>ERα (Hormone Receptor)</td>
<td>Clinical Studies</td>
<td>14.3 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis (\text{MORE Trial}) The effect of EVISTA on the incidence of breast cancer was assessed as a secondary safety endpoint in a randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women (see Clinical Studies [14.1]). After 4 years, EVISTA, 60 mg administered once daily, reduced the incidence of all breast cancers by 62%, compared with placebo (HR 0.38, 95% CI 0.22-0.67). EVISTA reduced the incidence of invasive breast cancer by 71%, compared with placebo (ARR 3.1 per 1000 women-years); this was primarily due to an 80% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. (See Table 7) (\text{CORE Trial}) The effect of EVISTA on the incidence of invasive breast cancer was evaluated for 4 additional years in a follow-up study conducted in a subset of postmenopausal women originally enrolled in the MORE osteoporosis treatment trial. Women were not re-randomized; the treatment assignment from the osteoporosis treatment trial was carried forward. EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 56%, compared with placebo (ARR 1.95 per 1000 women-years); this was primarily due to a 63% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. There was no reduction in the incidence of ER-negative breast cancer. In the osteoporosis treatment trial and the follow-up study, there was no difference in incidence of noninvasive breast cancer between the EVISTA and placebo groups. In a subset of postmenopausal women followed for up to 8 years from randomization in MORE to the end of CORE, EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 44% compared with placebo (absolute risk reduction [ARR] 1.2 per 1000 women-years); this was primarily due to a 55% reduction in estrogen receptor (ER)-positive invasive breast cancer in the EVISTA group compared with placebo (ARR 1.2 per 1000 women-years). There was no reduction in ER-negative invasive breast cancer. Table 8 presents efficacy and selected safety outcomes. (See Table 8)</td>
</tr>
<tr>
<td>022145, 03/05/2018</td>
<td>Raltegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12.5 Pharmacogenomics UGT1A1 Polymorphism There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult subjects with (28^2/28^2) 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 UGT1A1 genotype polymorphisms.</td>
</tr>
<tr>
<td>103846, 06/13/2016</td>
<td>Rasburicase (1)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS</td>
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<tr>
<td><strong>CONTRAINDICATIONS</strong></td>
<td></td>
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<tr>
<td>Elitek is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) [see Boxed Warning, Warnings and Precautions (5.2)].</td>
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<tr>
<td><strong>WARNINGS AND PRECAUTIONS</strong></td>
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<tr>
<td>5.2 Hemolysis</td>
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<tr>
<td>Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in &lt;1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Boxed Warning, Contraindications (4)].</td>
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<tr>
<td>5.3 Methemoglobinemia</td>
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<tr>
<td>Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek if methemoglobinemia occurs (4, 5.3).</td>
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<tr>
<td>5.4 Interference with Uric Acid Measurements</td>
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<tr>
<td>Elitek can result in 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)].</td>
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<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>1 INDICATIONS AND USAGE KISQALI is indicated in combination with: • an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or • fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.</td>
</tr>
<tr>
<td>020272, 03/01/2016</td>
<td>Risperidone</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>7 DRUG INTERACTIONS 7.11 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs [see Clinical Pharmacology (12.3)]. Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (in&lt;70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. (…)</td>
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<tr>
<td>103705, 08/12/2014</td>
<td>Rituximab</td>
<td>Oncology</td>
<td>MS4A1 (CD20 antigen)</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE 1.1 Non–Hodgkin's Lymphoma (NHL) Rituxan (rituximab) is indicated for the treatment of patients with: • Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. • Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy. • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy. • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. 1.2 Chronic Lymphocytic Leukemia (CLL) Rituxan (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL. 2 DOSAGE AND ADMINISTRATION 2.2 Recommended Dos e for Non-Hodgkin’s Lymphoma (NHL) The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules: • Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL Administer once weekly for 4 or 8 doses. • Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL Administer once weekly for 4 doses. • Previously Untreated, Follicular, CD20-Positive, B-Cell NHL Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses. • Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy. Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses. • Diffuse Large B-Cell NHL Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions. 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience in Lymphoid Malignancies Cytopenias and hypogammaglobulinemia (…) Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [See Clinical Studies (14.1)]. Most patients received Rituxan 375 mg/m² weekly for 4 doses. (…) 8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use Low-Grade or Follicular Non-Hodgkin’s Lymphoma Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. 14 CLINICAL STUDIES 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients. (…) 14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,062 patients. (…)</td>
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<td>02/24/08, 01/15/2019</td>
<td>Rivaroxaban</td>
<td>Cardiology</td>
<td>FS (Factor V Leiden)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.3 Reduction in the Risk of Recurrence of DVT and/or PE EINSTEIN CHOICE Study (…) 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 atrial fibrillation (19%), peripheral arterial disease (18%), pulmonary disease (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>02/20/03, 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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| 020533, 11/02/2018                   | Ropivacaine (2) | Anesthesiology | Nonspecific (Congenital Methemoglobinemia) | Warnings | WARNINGS Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for signs and symptoms of methemoglobinemia is recommended. (…)
| 021366, 05/27/2016                  | Rosuvastatin | Endocrinology     | SLCO1B1 Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY |
| 209115, 04/06/2018                   | Rucaparib (1) | Oncology          | BRCA | 1 INDICATIONS AND USAGE 1.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies 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)).
|                                      |                |                   |     | 2 DOSAGE AND ADMINISTRATION 2.3 Patient Selection for Treatment of BRCA-mutated Ovarian Cancer 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: http://www.fda.gov/CompanionDiagnostics.
|                                      |                |                   |     | 6 ADVERSE REACTIONS 6.1 Clinical Trials Experience (…) Rubraca 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single-arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had BRCA-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197). (…) 8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use In clinical studies 40% (297/749) of patients with ovarian cancer treated with Rubraca were 65 years of age or older and 9% (65/749) were 75 years or older. Grade 3-4 adverse reactions occurred in 65% of patients 65 years or older and in 63% of patients 75 years or older. For patients 65 years or older, the most common Grade 3-4 adverse reactions were anemia, fatigue/asthenia, and ALT/AST increase. No major differences in safety were observed between these patients and younger patients for the maintenance treatment of recurrent ovarian cancer or for the treatment of BRCA-mutated ovarian cancer after two or more chemotherapies.
|                                      |                |                   |     | 14 CLINICAL STUDIES (…) Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564), and the FoundationFocus™ Cdx BRCA LOH test (n=518). Of the samples evaluated with both tests, homologous recombination deficiency (HRD) positive status (as defined by the presence of a deleterious BRCA mutation or high genomic loss of heterozygosity) was confirmed in 94% (313/332) of HRD-positive patients determined by the CTA; and of these, tumor BRCA (tBRCA) mutant status was confirmed by the FoundationFocus™ Cdx BRCA LOH test for 94% (186/196) of the tBRCA patients. Blood samples for 94% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the tBRCA patients had a germline BRCA mutation and 30% (56/186) had a somatic BRCA mutation. ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rubraca as compared with placebo in all patients, and in the HRD and tBRCA subgroups. Results from a blinded independent radiology review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (with 22% of events). (see Table 6, Figures 1, 2, and 3) 14.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies The efficacy of Rubraca was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials. Study 10 (NCT01482715) and ARIEL2 (NCT01893344), in patients with advanced BRCA-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 108 patients received Rubraca 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and IRR according to RECIST v1.1. The median age of the patients was 59 years (range: 33 to 84), the majority were White (78%), and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had received 3 or more prior lines of platinum-based chemotherapy. There were 18/106 patients (17%) who had deleterious BRCA mutations detected in tumor tissue and not in whole blood.

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<td>209115, 04/06/2018</td>
<td>Rucaparib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Specific Populations CYP Enzyme Polymorphism Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.</td>
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<td>209115, 04/06/2018</td>
<td>Rucaparib (3)</td>
<td>Oncology</td>
<td>CYP1A2</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Specific Populations CYP Enzyme Polymorphism Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.</td>
</tr>
<tr>
<td>020478, 03/11/2014</td>
<td>Sevoflurane</td>
<td>Anesthesiology</td>
<td>RYR1</td>
<td>Warnings</td>
<td>WARNINGS Malignant Hyperthermia In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Sevoflurane can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia, and hypovolemia. In clinical trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these cases have been fatal. Treatment of malignant hyperthermia includes discontinuation of triggering agents (e.g., sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), and application of supportive therapy. Supportive therapy may include efforts to restore body temperature, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.</td>
</tr>
<tr>
<td>205123, 02/14/2017</td>
<td>Simeprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C [cytosine] to T [thymine] substitution) is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor. Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with OLYSIO-containing regimens. (See Table 12 and 13)</td>
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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; 87% had baseline HCV RNA levels greater than 800000 IU/mL; 74% had METAVIR fibrosis score F0, F1, or F2; 64% had HCV genotype 1a, and 17% HCV genotype 1b; 29% had IL28B CC genotype, 56% IL28B CT genotype, and 15% IL28B TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a; in QUEST 2, 69% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b. SVR12 rates were lower in subjects with genotype 1a virus than the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. (See Table 17) (...)

Precautions

5.6 G6PD Deficiency

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

Table of Pharmacogenomic Biomarkers in Drug Labeling

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- Sodium Nitrite
- Toxicology
- G6PD

5 Warnings and Precautions

- 5.6 G6PD Deficiency

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| 020752, 03/31/2009                     | Sodium Phenylbutyrate | Inborn Errors of Metabolism | ASS1, CPS1, OTC (Urea Cycle Disorders) | Indications and Usage, Dosage and Administration | INDICATIONS AND USAGE

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

**5 WARNINGS AND PRECAUTIONS**

5.1 Hypotension

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

5.2 Methemoglobinemia

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

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

**INDICATIONS AND USAGE**

BUPHENYL® is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a lifethreatening 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% (4/7 patients tested). (...)

(...)

In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98%. (...)

**DOSE AND ADMINISTRATION**

For oral use only.

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

**NUTRITIONAL MANAGEMENT**

(...)

At the recommended dose of sodium phenylbutyrate, it is suggested that infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period.

Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake. From 4 months to 1 year of age, it is recommended that the infant receive at least 1.4 g/kg/day, but 1.7 g/kg/day is advisable. From 1 to 3 years of age, the protein intake should not be less than 1.2 g/kg/day; 1.4 g/kg/day is advisable during this period. For neonatal-onset patients with carbamylphosphate synthetase deficiency or ornithine transcarbamylase deficiency who are at least 6 months of age, it is recommended that the daily protein intake be equally divided between natural protein and supplemental essential amino acids.

Patients with argininosuccinic acid synthetase deficiency and those with late-onset disease (partial deficiencies, including females heterozygous for ornithine transcarbamylase), initially may receive a diet containing the age-determined minimal daily natural protein allowance. The protein intake may be increased as tolerated and determined by plasma glutamine and other amino acid levels. However, many patients with partial deficiencies avoid dietary protein.

Citrulline supplementation is required and recommended for patients diagnosed with neonatal-onset deficiency of carbamylphosphate synthetase or ornithine transcarbamylase; citrulline daily intake is recommended at 0.17 g/kg/day or 3.8 g/m²/day.

The free-base form of arginine may be used instead of citrulline in patients with milder forms of carbamylphosphate synthetase and ornithine transcarbamylase deficiency (daily intake is recommended at 0.17 g/kg/day or 3.8 g/m²/day).

Arginine supplementation is needed for patients diagnosed with deficiency of argininosuccinic acid synthetase; arginine (free base) daily intake is recommended at 9.4–17.0 g/m²/day or 8.8–15.4 g/m²/day.

**14 CLINICAL STUDIES**

**14.2 Clinical Trials in Subjects with Genotype 1 or 4 HCV**

**Treatment-Naïve Adults — NEUTRINO (Study 1)**

(...)

SVR12 rates were 99% (89/90) in subjects with genotype 1 or 4 HCV and baseline IL28B C/C allele and 87% (200/230) in subjects with genotype 1 or 4 HCV and baseline IL28B non-C/C alleles. It is estimated that the SVR12 in patients who previously failed pegylated interferon and ribavirin therapy will approximate the observed SVR12 in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment (Table 9). The SVR12 rate in the NEUTRINO trial in genotype 1 subjects with IL28B non-C/C alleles, HCV RNA greater than 800,000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52). (See Table 9)

**14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1**

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| 208341, 02/14/2017                     | Sofosbuvir and Velpatasvir | Infectious Diseases | IFNL3 (IL28B) | Clinical Studies | 14 CLINICAL STUDIES

### 14.2 Clinical Trials in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis

Genotype 1, 2, 4, 5, and 6 HCV Infected Adults (ASTRAL-1)

- Demographics and baseline characteristics were balanced between the EPCLUSA and placebo group. Of the 740 treated subjects, the median age was 56 years (range: 18 to 82); 60% of the subjects were male; 76% were White; 9% were Black; 21% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 16%, 5%, and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced.

Genotype 2 HCV Infected Adults (ASTRAL-2)

- Demographics and baseline characteristics were balanced across the two treatment groups. Of the 266 treated subjects, the median age was 58 years (range: 23 to 81); 56% of the subjects were male; 88% were White; 7% were Black; 33% had a baseline body mass index at least 30 kg/m²; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels at least 800,000 IU/mL; 14% had compensated cirrhosis; and 15% were treatment-experienced.

Genotype 3 HCV Infected Adults (ASTRAL-3)

- Demographics and baseline characteristics were balanced across the treatment groups. Of the 552 treated subjects, the median age was 52 years (range: 19 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

### 14.3 Clinical Trials in Subjects with Decompensated Cirrhosis

- Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m². The proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

### 14.2 Clinical Trials in HCV DAA-Experienced Subjects

NS5A Inhibitor-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis (POLARIS-1)

- Demographics and baseline characteristics were generally balanced across treatment groups. Of the 415 treated subjects, the median age was 59 years (range: 27 to 84); 77% of the subjects were male; 81% were White; 14% were Hispanic or Latino; 33% had a baseline body mass index at least 30 kg/m²; the majority of subjects had genotype 1 (72%) or genotype 3 (19%) HCV infection; 82% had a non-CC IL28B genotype (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; and 41% had compensated cirrhosis.

DAA-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis Who Had Not Received An NS5A Inhibitor (POLARIS-4)

- Demographics and baseline characteristics were generally balanced across treatment groups. Of the 333 treated subjects, the median age was 54 years (range: 24 to 85); 77% of the subjects were male; 87% were White; 9% were Black; 4% had a baseline body mass index at least 30 kg/m²; 82% had a non-CC IL28B genotype (CT or TT); 75% had baseline HCV RNA levels at least 800,000 IU/mL; and 46% had compensated cirrhosis.

### 14.4 Clinical Trials in Subjects with Decompensated Cirrhosis

- Demographics and baseline characteristics were generally balanced across treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

### 14.5 Clinical Trials in Subjects with Decompensated Cirrhosis

- Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

### 14.6 Clinical Trials in Subjects with Decompensated Cirrhosis

- Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

### 14.7 Clinical Trials in Subjects with Decompensated Cirrhosis

- Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

### 14.8 Clinical Trials in Subjects with Decompensated Cirrhosis

- Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White; 6% were Black; 42% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 76%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.
### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 12/2018**

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>017377, 07/16/2014</td>
<td>Sulfamethoxazole and Trimethoprim (1)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>017377, 07/16/2014</td>
<td>Sulfamethoxazole and Trimethoprim (2)</td>
<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<tr>
<td>007073, 03/04/2014</td>
<td>Sulfasalazine (1)</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>007073, 03/04/2014</td>
<td>Sulfasalazine (2)</td>
<td>Gastroenterology</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>210607, 08/08/2018</td>
<td>Tafenoquine</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>4 CONTRAINDICATIONS</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.2 G6PD Deficiency in Pregnancy and Lactation</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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</thead>
<tbody>
<tr>
<td>211651, 10/16/2018</td>
<td>Talazoparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for antimalaria during pregnancy (see Warnings and Precautions (5.2)). (...) 8.2 Lactation Risk Summary A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown (see Contraindications (4) and Clinical Considerations). There is no information regarding the presence of ARAKODA in human milk; the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition. Clinical Considerations Check the infant’s G6PD status before maternal breastfeeding commences. If an infant is G6PD-deficient, exposure to ARAKODA during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency or whose G6PD status is unknown, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose of ARAKODA. 8.3 Females and Males of Reproductive Potential Contraception ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus (see Warnings and Precautions (5.2)). Use in Specific Populations (8.1). Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA. 17 PATIENT COUNSELING INFORMATION G6PD Testing and Hemolytic Anemia Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia (see Warnings and Precautions (5.1)). 17.1 Lactation Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose (see Contraindications (4), Warnings and Precautions (5.2)). Use in Specific Populations (8.2).</td>
</tr>
</tbody>
</table>

| 211651, 10/16/2018 | Talazoparib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 

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</thead>
<tbody>
<tr>
<td>G21807, 09/25/2018</td>
<td>Tamoxifen (1)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>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)].</td>
</tr>
<tr>
<td>021807, 09/25/2018</td>
<td>SOLTAMOX</td>
<td>Indications and Usage, Adverse Reactions</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>1 INDICATIONS AND USAGE</td>
<td>SOLTAMOX is indicated for the treatment of adult patients with estrogen receptor-positive metastatic breast cancer.</td>
</tr>
</tbody>
</table>

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

**EMBRACA**

The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic Breast Cancer (gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer). 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) of the healthcare provider's choice (n=126) until disease progression or unacceptable toxicity. (…)

**EMBRACA Study (NCT01914775)**

Deleterious or Suspected Deleterious Germline BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer (gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer). EMBRACA (NCT01914775) 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, 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 (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system (CNS) metastasis (yes versus no). (…)

### 14 CLINICAL STUDIES

#### 14.2 Adjuvant Treatment of Breast Cancer

At a median follow-up of 33 months, the combination of anastrozole and tamoxifen did not demonstrate an efficacy benefit when compared to tamoxifen monotherapy in all patients as well as in the hormone receptor-positive subpopulation. The combination treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving anastrozole 1 mg and tamoxifen 20 mg monotherapy, respectively. (…)

### 12 CLINICAL PHARMACOLOGY

#### 12.5 Pharmacogenomics

The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women's Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.8 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultraport, 1.097 normal, 164 intermediate and 82 poor metabolizers (p<0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.

### 14 CLINICAL STUDIES

#### 14.2 Adjuvant Treatment of Breast Cancer

The Early Breast Cancer Trialists' 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 36,489 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 (>10 fmol/mg), 21% were ER-poor (<10 fmol/mg), and 31% were ER-unknown. Among 29,441 patients with ER-positive or ER-unknown breast cancer, 56% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen to chemotherapy. The recurrence-free rate at 10 years was 79.2% for tamoxifen vs. 64.3% for control (log-rank 2p <0.0001).

#### 14.3 Indications and Usage

**Breast cancer**

In women with ER-positive or ER-unknown breast cancer:

- With positive nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (log-rank 2p <0.0001).
- With negative nodes who received about 5 years of treatment, overall survival at 10 years was 84.9% for tamoxifen vs. 73.3% for control (log-rank 2p <0.0001).

**Breast cancer**

The recurrence-free rate at 10 years was 79.2% for tamoxifen vs. 64.3% for control (log-rank 2p <0.0001).

### Footnotes

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<td>Oncology</td>
<td>P5</td>
<td>Warnings and Precautions</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Thromboembolic Events (…) In a small substudy (N = 81) of the NSABP-1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations G20210A as a means to identify those who may not be appropriate candidates for tamoxifen therapy.</td>
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<td>Oncology</td>
<td>F2</td>
<td>Warnings and Precautions</td>
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<tr>
<td>Tamoxifen</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism: Tamoxifen is extensively metabolized by CYP450 enzymes, including CYP3A, CYP2D6, CYP2C9, CYP2C19, and CYP2B6. N-desmethyltamoxifen, formed predominately by CYP3A, is the major metabolite found in plasma. The pharmacological activity of N-desmethyltamoxifen is similar to that of tamoxifen. Endoxifen and 4-hydroxytamoxifen, identified as minor metabolites, have 100-fold greater affinity for the estrogen receptor and 30 to 100-fold greater potency in suppressing estrogen-dependent cell proliferation than tamoxifen. The polymorphic enzyme CYP2D6 is involved in the formation of endoxifen and 4-hydroxytamoxifen, and it is the key enzyme that catalyzes the formation of endoxifen from N-desmethyltamoxifen. Endoxifen concentrations may differ among patients because of various CYP2D6 genotypes [see Clinical Pharmacology (12.5)]. Phase 2 enzymes, such as SULT1A1, UGT2B7, and UGT1A4, are associated with tamoxifen clearance from plasma. 12.5 Pharmacogenomics The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women’s Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p&lt;0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers. 5 WARNINGS AND PRECAUTIONS 5.2 Drug Interactions Tamoxifen is extensively metabolized, mainly by CYP3A4 and CYP2D6. FLOMAX capsules 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. FLOMAX capsules should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terbinafine) inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers particularly at a dose higher than 0.4 mg (e.g., 0.8 mg) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].</td>
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14 CLINICAL STUDIES
14.2 Treatment-Naive Adults

Trial C211 (OPTIMIZE)

(…) SVR rates were similar for the T12 (daily) and T12 (q8h) groups within the genotypes and across subgroups determined by sex, race, ethnicity, body mass index, HCV genotype subtype, IL28B genotype, baseline HCV RNA (less than 800,000, greater than or equal to 800,000 IU per mL), and extent of liver fibrosis. However, there were small numbers of subjects enrolled in some key subgroups. (…)

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Drug Interactions
Cytochrome P450 Inhibition

Strong and Moderate Inhibitors of CYP3A4 or CYP2D6

(…) The effects of paroxetine (a strong inhibitor of CYP2D6) at 20 mg once daily for 9 days on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range 23 to 47 years). Concomitant treatment with paroxetine resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively [see Warnings and Precautions (5.2) and Drug Interactions (7.1)]. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PMs) as compared to extensive metabolizers (EM). A fraction of the population (about 7% of Caucasians and 2% of African Americans) are CYP2D6 PMs. Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when FLOMAX 0.4 mg is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, FLOMAX 0.4 mg capsules should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]. (…)
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<tbody>
<tr>
<td>012429, 05/23/2018</td>
<td>Thioguanine (1)</td>
<td>Oncology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings, Precautions, Clinical Pharmacology</td>
<td>Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient’s CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg [see Dosage and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. 8 USE IN SPECIFIC POPULATIONS 8.7 Poor or Extensive CYP2D6 Metabolizers Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dosage should be adjusted 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)].</td>
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<tr>
<td>012429, 05/23/2018</td>
<td>Thioguanine (2)</td>
<td>Oncology</td>
<td>NUDT15</td>
<td>Dosage and Administration, WARNINGS, PRECAUTIONS</td>
<td>(…) Patients with homozygous deficiency of either TPMT or NUDT15 enzyme typically require 10% or less of the standard thioguanine dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. Reduce the dosage based on tolerability.</td>
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<tr>
<td>011808</td>
<td>Thioridazine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Contraindications, Warnings, Precautions</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<td>022433, 09/23/2016</td>
<td>Ticagrelor</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Pharmacogenetics</td>
<td>In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status.</td>
</tr>
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<td>018894</td>
<td>Tolazamide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
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<td>Precautions</td>
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<td>021228, 07/13/2018</td>
<td>Tolterodine</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>5 WARNINGS AND PRECAUTIONS 5.9 Use in Patients with Congenital or Acquired QT Prolongation</td>
<td>In a study of the effect of tolterodine immediate release tablets on the QT interval [see CLINICAL PHARMACOLOGY (12.2)], the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. (…)</td>
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<td>7 DRUG INTERACTIONS 7.1 Potent CYP2D6 Inhibitors</td>
<td>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 (12.2)]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [see CLINICAL PHARMACOLOGY (12.3)].</td>
</tr>
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**Table of Pharmacogenomic Biomarkers in Drug Labeling**

*Last Updated: 12/2018*

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<tr>
<td></td>
<td>Toremifene</td>
<td>Oncology</td>
<td>ESR (Hormone Receptor)</td>
<td>Indications and Usage, Clinical Studies</td>
<td>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)].</td>
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<tr>
<td>020497, 05/12/2017</td>
<td>Tramadol</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Boxed Warning, Warnings, Precautions, Use in Specific Populations, Clinical Pharmacology</td>
<td><strong>BOXED WARNING</strong> 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 adenotonsillectomy. For a time it was thought one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenotonsillectomy (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). <strong>WARNINGS</strong> Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol or</td>
</tr>
<tr>
<td>020281, 08/29/2017</td>
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with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- ULTRAM is contraindicated for all children younger than 12 years of age (see CONTRAINDICATIONS).
- ULTRAM is contraindicated for post-operative management in pediatric patients 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 unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose (see PRECAUTIONS/Pediatric Use, OVERDOSAGE).

Nursing Mothers

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

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 genotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenaz Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see OVERDOSAGE). Therefore, individuals who are ultra-rapid metabolizers should not use ULTRAM.

PRECAUTIONS

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise caregivers that ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 years of age receiving ULTRAM to monitor for signs of respiratory depression (see WARNINGS).

USE IN SPECIFIC POPULATIONS

Pediatric Use The safety and effectiveness of ULTRAM in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol (see WARNINGS). In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isozyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

- ULTRAM is contraindicated for all children younger than 12 years of age (see CONTRAINDICATIONS).
- ULTRAM is contraindicated for post-operative management in pediatric patients 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 unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

CLINICAL PHARMACOLOGY

Metabolism

Approximately 7% of the population has reduced activity of the CYP2D6 isozyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, destmethylmorphine, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower. Poor / Extensive Metabolizers, CYP2D6

The formation of the active metabolite, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isozyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, destmethylmorphine and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower.
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<tr>
<td></td>
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<td>MEKINIST is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see Dosage and Administration (2.1), (2.3)].</td>
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<tr>
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<td>1.9 BRAF V600E Mutation-Positive Metastatic NSCLC MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.4)].</td>
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<td>1.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)].</td>
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<td>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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. 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: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>. Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.4)].</td>
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<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Unresectable or Metastatic BRAF V600E Mutation Positive Melanoma MEKINIST Administered as a Single Agent 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 (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 236 patients with previously untreated melanoma with BRAF V600E or V600K mutations receiving MEKINIST (N = 119) and dabrafenib (N = 117) [see Clinical Studies (14.2)]. Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma The safety of MEKINIST when administered with dabrafenib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-d 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 BRF113508). 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).</td>
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<td>12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Administration of 1 mg and 2 mg MEKINIST to patients with BRAF V6000 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). 13.3 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.</td>
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<td>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.</td>
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|… 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 from dabrafenib to MEKINIST. In the COMBI-d study, 423 patients were randomized to MEKINIST plus dabrafenib and 432 to placebo. Median age was 51 years (range: 18 to 89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0 or 1. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%), BRAF V600E mutation (91%), BRAF V600K mutation (9%), macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 13)…
|… In Study BRF113928 (NCT01336634), the safety and efficacy of dabrafenib alone or administered with MEKINIST were evaluated in a multicenter, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy).…
|… In Study BRF113928 (NCT01336634), the safety and efficacy of dabrafenib alone or administered with MEKINIST were evaluated in a multicenter, international trial in 40 patients with BRAF V600E or V600K mutations as detected by the ThermoFisher Scientific assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive MEKINIST 2 mg once daily in combination with dabrafenib 150 mg twice daily or two placebos for up to 1 year. Enrolment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable intrathoracic metastases, distant metastatic disease, or prior systemic anticancer treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIia, Iib, IIIc, or IV).…
|… 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 BRF113928, non-cutaneous malignancies occurred in 1.1% (1/93) of patients receiving MEKINIST with dabrafenib. |
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<td>103792, 11/29/2018</td>
<td>Trastuzumab (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>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>
</tr>
</tbody>
</table>

1. **INDICATIONS AND USAGE**
   1.1 **Adjuvant Breast Cancer**
   - Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer.
   - As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel.
   - With docetaxel and carboplatin.
   - As a single agent following multi-modality anthracycline based therapy.

1.2 **Metastatic Breast Cancer**
   - Herceptin is indicated:
     - In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer.
     - As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

1.3 **Metastatic Gastric Cancer**
   - Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

2. **DOSAGE AND ADMINISTRATION**
   2.1 **Patient Selection**
   - Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)].
   - Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.
   - Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.
   - Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

12. **CLINICAL PHARMACOLOGY**
   12.2 **Pharmacodynamics**
   - Cardiac Electrophysiology:
     - The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors.
     - Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTc 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 4563 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 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**

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

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

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 12). (…)

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</table>
| 103792, 11/29/2018 | Trastuzumab (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES 14.1 Adjuvant Breast Cancer Study 4 (…)

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| 205382, 10/20/2017                     | Umeclidinium | Pulmonary | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Umeclidinium and Cytochrome P450 2D6:
In vitro metabolism of umclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing to normal (ultrarapid, extensive, and intermediate metabolizers) and CYP2D6 poor metabolizer subjects (Figure 1). |
| 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-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances. |
| 209241, 04/11/2017                     | Valbenazine | 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 (8.6), Clinical Pharmacology (12.3)]. |
| 018081, 10/05/2017                     | 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 Huttonlocher 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)].

4 CONTRAINdications
(…), Depakene is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttonlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder [see Warnings and Precautions (5.1)]. (…)

5 WARNINGS AND PRECAUTIONS
5.1 Hepatotoxicity
Patients with Known or Suspected Mitochondrial Disease
Depakene is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder [see Contraindications (4)]. Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttonlocher Syndrome) at a

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<td>018081, 10/05/2017</td>
<td>Valproic Acid (2)</td>
<td>Neurology</td>
<td>Nonspecific (Urea Cycle Disorders)</td>
<td>Contraindications, Warnings and Precautions</td>
<td>higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene for the development of acute liver injury with regular clinical assessments and serum liver test monitoring. The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug [see Boxed Warning and Contraindications (4)].</td>
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| 202429, 11/06/2017                     | Vemurafenib (1) | Oncology | BRAF | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information | 1 INDICATIONS AND USAGE
1.1 Unresectable or Metastatic Melanoma
ZELBORAF® is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].
1.2 Erdheim-Chester Disease
ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. |

| 2. DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Confirm the presence of BRAF V600E mutation in melanoma tumor specimens prior to initiation of treatment with ZELBORAF [see Warnings and Precautions (5.2)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at http://www.fda.gov/CompanionDiagnostics. |
| 3. 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 substudy in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [see Clinical Pharmacology (12.2)]. (... ) |
| 6. ADVERSE REACTIONS
6.1 Clinical Trials Experience |

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<td>This section describes adverse drug reactions (ADRs) identified from analyses of Trial 1 and Trial 2 [see Clinical Studies (14)]. (…) Erdheim-Chester Disease (ECD)</td>
<td>This section describes adverse reactions identified from analyses of Trial 4 [see Clinical Studies (14)]. In Trial 4, 22 patients with BRAF V600 mutation-positive ECD received ZELBORAF 960 mg twice daily. The median treatment duration for ECD patients in this study was 14.2 months. Table 3 presents adverse reactions reported in at least 20% of BRAF V600 mutation-positive ECD patients treated with ZELBORAF. In Trial 4, the most commonly reported adverse reactions (&gt; 50%) in patients with BRAF V600 mutation-positive ECD treated with ZELBORAF were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The most common (≥ 10%) Grade 3 adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculo-papular, and arthralgia. (…)</td>
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### 8 USE IN SPECIFIC POPULATIONS

#### 8.4 Pediatric Use

The safety and effectiveness of ZELBORAF in pediatric patients have not been established. Vemurafenib was studied in 6 adolescents 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 adolescents patients was generally similar to that in adults.

#### 12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

#### 14 CLINICAL STUDIES

14.1 Treatment-Naïve 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 (…) 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 Metastatic 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)]. Patients with Erdheim-Chester Disease (ECD) An open-label, multicenter, single-arm, multiple cohort study of ZELBORAF (Trial 4) was conducted in patients ≥ 16 years of age with non-melanoma BRAF V600 mutation-positive diseases. (…) | Treatment-Naïve Patients with BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma | (….) | | | |

#### 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)]. (…) | (…) | | | | |

### Adverse Reactions

#### 6.2 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. Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Progression of pre-existing chronic myelomonocytic leukemia with NRAS mutation [see Warnings and Precautions (5.1)]. (…) | (…) | | | | |

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<td>9.6 Age and Gender</td>
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<td>A population pharmacokinetic analysis of 404 Effexor-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see Dosage and Administration (2.6)) (see Table 15). (See Figure 3)</td>
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**12 CLINICAL PHARMACOLOGY**

12.3 Pharmacokinetics

Metabolism and elimination

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels (poor metabolizers) had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 levels (extensive metabolizers) [see Use in Specific Populations 8.7].

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<td>Oncology</td>
<td>TP53</td>
<td>Clinical Studies</td>
<td>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 17) (…)</td>
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cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose

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

6 ADVERSE REACTIONS

Integrated Summary of Safety in Relapsed and/or Refractory Ph- Adult Acute Lymphoblastic Leukemia

Marqibo, at a dose of 2.25 mg/m² weekly, was studied in a total of 83 patients in two trials: study 1 and study 2. Adverse reactions were observed in 100% of

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 [see Drug Interactions (7)].

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

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Metabolism and Elimination

Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and

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

Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

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Metabolism

The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic cytochrome P-450 (CYP450) microsomal enzymes to inactive (predominantly route) and by reduced metabolites to reduced anticoagulant activity. Identified metabolites of warfarin include dehydrowarfarin, two diastereoisomer alcohols, and 4', 6', 7', 8', and 10'-hydroxywarfarin. The CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 1A2, and 3A4. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the in vivo anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance [see Clinical Pharmacology (12.5)].

12.5 Pharmacogenomics

CYP2C9 and VKORC1 Polymorphisms  The S-enantionomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9, and *11 alleles in Caucasians.

Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle through inhibition of VKOR, a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (e.g., −1639G>A) have been associated with variable warfarin dose requirements. VKORC1 and CYP2C9 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)].

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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)

CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

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PROS1

An anticoagulation effect generally occurs within 24 hours after warfarin administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN may become more pronounced as effects of daily maintenance doses overlap. This is consistent with the half-lives of the affected vitamin K-dependent clotting factors and anticoagulation proteins: Factor II - 60 hours, VII - 4 to 6 hours, IX - 24 hours, X - 48 to 72 hours, and proteins C and S are approximately 8 hours and 30 hours, respectively.

5 WARNINGS AND PRECAUTIONS

5.7 Other Clinical Settings with Increased Risks

In the following clinical settings, the risks of COUMADIN therapy may be increased:

- Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimize the incidence of tissue necrosis in these patients. (…)

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

An anticoagulation effect generally occurs within 24 hours after warfarin administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN may become more pronounced as effects of daily maintenance doses overlap. This is consistent with the half-lives of the affected vitamin K-dependent clotting factors and anticoagulation proteins: Factor II - 60 hours, VII - 4 to 6 hours, IX - 24 hours, X - 48 to 72 hours, and proteins C and S are approximately 8 hours and 30 hours, respectively.

5 WARNINGS AND PRECAUTIONS

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In the following clinical settings, the risks of COUMADIN therapy may be increased:

PROCs

These are not necessarily exhausted by the CDER review division.

† Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language.

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

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

**Last Updated: 12/2018**

<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>
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<td></td>
<td></td>
<td>(...) Deficiency in protein C-mediated anticoagulant response: COUMADIN reduces the synthesis of the naturally occurring anticoagulants, protein C and protein S. Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimize the incidence of tissue necrosis in these patients. (...)</td>
</tr>
</tbody>
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12 CLINICAL PHARMACOLOGY

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