Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2018

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: Pharmacogenomic Biomarkers in Drug Labeling

<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>020977, 03/20/2017</td>
<td>Abacavir</td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>BOXED WARNING</td>
<td>WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Hypersensitivity Reactions</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with ZIAGEN® (abacavir)</td>
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<td>Patients who carry the HLA-B<em>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</em>5701 allele [see Warnings and Precautions (5.1)].</td>
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<td></td>
<td>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)].</td>
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<tr>
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<td></td>
<td>All patients should be screened for the HLA-B<em>5701 allele prior to initiating therapy with ZIAGEN or relaunch of therapy with ZIAGEN, unless patients have a previously documented HLA-B</em>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)].</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>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)].</td>
</tr>
</tbody>
</table>

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

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

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

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</table>
| 208716, 09/28/2017                     | Abemaciclib (1) | Oncology          | ESR, PGR  | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
VERZENIO™ (abemaciclib) is indicated:  
- 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 HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. |
| 208716, 08/28/2017                     | Abemaciclib (2) | Oncology          | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 1 INDICATIONS AND USAGE
VERZENIO™ (abemaciclib) is indicated:  
- 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 HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. |

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<tbody>
<tr>
<td>125427, 07/25/2016</td>
<td>Ado-Trastuzumab Emtansine</td>
<td>Oncology</td>
<td>ERβ2 (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. 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. (…)</td>
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<tr>
<td>201292, 01/12/2018</td>
<td>Afatinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies</td>
<td>1 INICATIONS AND USAGE 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)].</td>
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### 1 INDICATIONS AND USAGE

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with ALECENSA based on the presence of ALK positivity in tumor specimens (see Indications and Usage (1) and Clinical Studies (14)).

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

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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. (…)

#### 14 CLINICAL STUDIES

**14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer**

The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage Iib with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic therascreen® EGFR RGQ PCR Kit, which is FDA-approved for selection of patients for GILOTRIF treatment. Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

Pre-specified exploratory subgroup analyses were conducted according to the stratification factor of EGFR mutation category. See Figure 2 and text below Figure 2.

**Overall Response Rate In Other EGFR Mutations**

The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (L788I, 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 8 [NCT01121383]). 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 cetuximab 750 mg/m² plus pemetrexed 500 mg/m² every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR RGQ 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 RGQ 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 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage Iib disease, and 88% had received no prior systemic therapy for advanced or metastatic disease.

The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.

#### 14.2 ALK-Positive Metastatic NSCLC

**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. (…)

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| 05/02/2014                             | Amitriptyline | Psychiatry | CYP2D6 | Precautions | Drugs Metabolized by P450 2D6

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: NCT028761 (NCT01588028) and NCT23373 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. (…) PRECAUTIONS
Drugs Metabolized by P450 2D6
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. (…) 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 zoledronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture. (…) 7 DRUG INTERACTIONS
7.1 Tamoxifen
Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial [see Clinical Studies (14.1)]. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole. (…) * Therapeutic areas do not necessarily reflect the CDER review division.
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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>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>021912, 02/27/2014</td>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-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>Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2C6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inhibitor is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of a strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response. (See Table 2)</td>
</tr>
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<tr>
<td>761034, 06/28/2018</td>
<td>Atezolizumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
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<td>TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:</td>
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<td>- are not eligible for cisplatin-containing chemotherapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), or</td>
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<td>- are not eligible for any platinum-containing chemotherapy regardless of level of tumor PD-L1 expression, or</td>
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<td>- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>NSCLC</td>
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<td>(…) The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see Clinical Studies (14.2)]. (…)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Specific Populations</td>
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<td>Age (21–89 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 &lt; 1.0 to 1.5 × ULN and any AST), level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab. (…)</td>
</tr>
</tbody>
</table>

**2 DOSE ADMINISTRATION**

**2.4 Dose Adjustments for CYP450 Considerations**

Refer to the prescribing information for oral aripiprazole for recommendations regarding dosage adjustments due to drug interactions, for the first 21 days when the patient is taking oral aripiprazole concomitantly with the first dose of ARISTADA. Once stabilized on ARISTADA, refer to the dosing recommendations below for patients taking CYP 2D6 inhibitors, CYP 3A4 inhibitors, or CYP 3A4 inducers:

- No dosage changes recommended for ARISTADA, if CYP 450 modulators are added for less than 2 weeks.
- Make dose changes to ARISTADA if CYP 450 modulators are added for greater than 2 weeks. (See Table 4)

**8 USE IN SPECIFIC POPULATIONS**

**8.6 CYP2D6 Poor Metabolizers**

Dose adjustment is recommended in known CYP 2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3-4% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

**12 CLINICAL PHARMACOLOGY**

**12.3 Pharmacokinetics**

Metabolism and Elimination

(…) Elimination of aripiprazole is mainly through hepatic metabolism involving CYP 3A4 and CYP 2D6. Dose adjustments are recommended in CYP 2D6 poor metabolizers due to high aripiprazole concentrations [see Dosage and Administration (2.4)].

Drug Interaction Studies

No specific drug interaction studies have been performed with ARISTADA. The drug interaction data provided below is obtained from studies with oral aripiprazole.

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cm ax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP 2D6 and CYP 3A4 inhibitors. After oral administration, a 3-fold increase in mean Cm ax and AUC values at steady-state is expected in poor metabolizers of CYP 2D6 administered with strong CYP 3A4 inhibitors. (See Figure 1, 2, and 3)

Specific Population Studies

A population pharmacokinetic analysis showed no effect of sex, race or smoking on ARISTADA pharmacokinetics [see Use in Specific Populations (8.8)].

Exposures of aripiprazole and dehydro-aripiprazole using oral aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. (See Figure 4 and 5)

**8.8 ELIMINATION**

**8.8.2 CYP2D6**

(…) Elimination of aripiprazole is mainly through hepatic metabolism involving CYP 3A4 and CYP 2D6. Dose adjustments are recommended in CYP 2D6 poor metabolizers due to high aripiprazole concentrations [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

**8 USE IN SPECIFIC POPULATIONS**

**8.6 CYP2D6 Poor Metabolizers**

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**12 CLINICAL PHARMACOLOGY**

**12.3 Pharmacokinetics**

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Last Updated: 06/2018

<table>
<thead>
<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
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<th>Biomarker†</th>
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### 14 CLINICAL STUDIES

#### 14.1 Urothelial Carcinoma

**Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma**

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 98 patients, 42% 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 58% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumor-infiltrating IC covering < 5% of the tumor area).

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1.

### 14.2 Metastatic Non-Small Cell Lung Cancer

The efficacy of TECENTRIQ was evaluated in a multinational, 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 tumors (i.e., cisplatin or carboplatin with gemcitabine), and platinum-based chemotherapy alone (comparator). Both cisplatin-eligible and cisplatin-ineligible patients were included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The Independent Data Monitoring Committee (IDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of ≤ 5% when treated with TECENTRIQ monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The IDMC recommended closure of the monotherapy arm to further accrual of patients with low PD-L1 expression, however, no other changes were recommended for the study, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

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

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

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1.

### 2 DOSEAGE AND ADMINISTRATION

**2.4 Dosing in Specific Populations**

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

### 5 WARNINGS AND PRECAUTIONS

#### 5.12 Laboratory Tests

Routine laboratory tests are not required. CYP2D6 metabolism- Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs.
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| 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 events occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: insomnia (11% of PMs, 6% of EMs); weight decreased (7% of PMs, 4% of EMs); constipation (11% of PMs, 7% of EMs); feeling jittery (5% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); middle insomnia (3% of PMs, 1% of EMs); conjunctivitis (3% of PMs, 1% of EMs); syncope (3% of PMs, 1% of EMs); early morning awakening (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs); sedation (4% of PMs, 2% of EMs). (…)

Adult Clinical Trials

(…) The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metaboliser (EM) patients: vision blurred (4% of PMs, 1% of EMs); dry mouth (35% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs); feeling jittery (5% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (8% of PMs, 2% of EMs); hyperhidrosis (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of EMs). (…)

7 DRUG INTERACTIONS

7.2 Effect of CYP2D6 Inhibitors on Atomoxetine

In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold andCss, max is about 3- to 4-fold greater than atomoxetine alone. In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of STRATTERA on QTc prolongation was evaluated in a randomized, double-blind, 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 andCss, max 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-Demethylatomoxetine 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).

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| NDA/ANDA
drug label version | Drug | Therapeutic
area | Biomarker† | Labeling
sections | Labeling text† |
|-------------------|------|-----------|----------|-----------------|-----------------|
| 210238, 05/21/2018 | Avatrombopag | (1) | G6PD | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

DOPTENET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with DOPTENET. Consider the potential increased thrombotic risk when administering DOPTENET 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).

DOPTENET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |
| 210238, 05/21/2018 | Avatrombopag | (2) | F5 (Factor V Leiden) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

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| 210238, 05/21/2018 | Avatrombopag | (3) | PROC | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

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| 210238, 05/21/2018 | Avatrombopag | (5) | SERPINC1 (Antithrombin III) | Warnings and Precautions | 5 WARNINGS AND PRECAUTIONS 5.1 Thrombotic/Thromboembolic Complications

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DOPTENET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. |

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of atomoxetine. Atomoxetine concentrations are approximately 10-fold and Css, max is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of atomoxetine. Atomoxetine concentrations are approximately 10-fold and Css, max is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of atomoxetine.

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<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 (65%) or 1 (44%). Seventy-five percent of patients were 65 years or older. 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive (≥ 1% of tumor cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCC) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCC. Efficacy results are presented in Table 4. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCC. (See Table 4)</td>
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<tr>
<td>016324, 02/06/2014</td>
<td>Azathioprine</td>
<td>Rheumatology</td>
<td>TPMT</td>
<td>Dosage and Administration, Warnings, Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology</td>
<td>DOSAGE AND ADMINISTRATION TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING IMURAN. TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity from IMURAN if conventional doses are given. Physicians may consider alternative therapies for patients who have low or absent TPMT activity (homozygous for non-functional alleles). IMURAN should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction.</td>
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| 206256, 07/03/2014                     | Belinostat            | Oncology          | UGT1A      | Dosage and Administration, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION  
2.3 Patients with Reduced UGT1A1 Activity  
Reduce the starting dose of Belinostat to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele [see Clinical Pharmacology (12.5)]. |
| 210498, 06/27/2018                     | Binimetinib (1)       | Oncology          | BRAF       | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE  
MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)]. |

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| 210408, 06/27/2018                    | Binimetinib (2) | Oncology          | UGT1A1     | 12 CLINICAL PHARMACOLOGY | 12.3 Pharmacokinetics Drug Interaction Studies Clinical Studies
Effect of UGT1A1 Inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Simulations predict similar Cmax of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor). |
| 125507, 08/30/2016                    | Blinatumomab | Oncology          | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE
BLINCYTO is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) [see Dosage and Administration (2.1)]. |
| 203341, 11/17/2016                    | Bosutinib | Oncology          | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies | 1 INDICATIONS AND USAGE
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. |
| 202258, 01/30/2017                    | Boceprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to 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 higher SVR rates with regimens containing VICTRELIS. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the study population relative to the overall trial population. (See Table 9) |
| 125388, 09/28/2016                    | Brentuximab Vетодin | Oncology          | ALK | Clinical Studies | 14 CLINICAL STUDIES
14.2 Systemic Anaplastic Large Cell Lymphoma
Clinical Trial in Relapsed sALCL (Study 2) (…) The 58 patients ranged in age from 14-76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 20% 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. (…) |

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<td>205422, 02/23/2017</td>
<td>Brexpiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION</td>
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<tr>
<td></td>
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<td></td>
<td>2.5 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inhibitors or Inducers</td>
</tr>
<tr>
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<td>Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). If the coadministered drug is discontinued, adjust the REXULTI dosage to its original level, if the coadministered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks</td>
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<td>[see Drug Interactions (7.1), Clinical Pharmacology (12.3)].  (See Table 1)</td>
</tr>
<tr>
<td>208772, 04/28/2017</td>
<td>Brigatinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
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<td>ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. (…)</td>
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<td></td>
<td>6 ADVERSE REACTIONS</td>
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<td></td>
<td>6.1 Clinical Trial Experience</td>
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<td>(…) The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least one dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. (…)</td>
</tr>
<tr>
<td>208838, 06/03/2016</td>
<td>Brivaracetam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<tr>
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<td></td>
<td>12.3 Pharmacokinetics</td>
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<td></td>
<td>Metabolism</td>
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<td>Brivaracetam is primarily metabolized by hydroxylation of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydroxylation reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.</td>
</tr>
<tr>
<td>009388, 12/24/2003</td>
<td>Busulfan</td>
<td>Oncology</td>
<td>BCR-ABL1 (Philadelphia chromosome)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
</tr>
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<td>(…) Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph) chromosome. Also, the so-called “juvenile” type of chronic myelogenous leukemia, typically occurring in young children and associated with the absence of a Philadelphia chromosome, responds poorly to busulfan. The drug is of no benefit in patients whose chronic myelogenous leukemia has entered a “blastic” phase. (…)</td>
</tr>
<tr>
<td>203756, 05/20/2016</td>
<td>Cabozantinib</td>
<td>Oncology</td>
<td>RET</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td>(…) Of 330 patients randomized, 67% were male, the median age was 55 years, 23% were 65 years or older, 89% were white, 54% had a baseline ECOG performance status of 0, and 92% had undergone a thyroidectomy. The RET mutation status determined by a research use assay was positive in 51%, negative in 14%, and was unknown in 35%. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI. (…)</td>
</tr>
<tr>
<td>020866, 12/14/2016</td>
<td>Capecitabine</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
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<td></td>
<td>5.4 Dihydropyrimidine Dehydrogenase Deficiency</td>
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<td>Based on postmarketing reports, patients with certain homozgyous or certain compound heterozygous mutations in the DPYD gene that result in complete or near complete absence of DPYD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPYD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA. Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPYD activity.</td>
</tr>
</tbody>
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<th>Labeling Text‡</th>
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<tbody>
<tr>
<td>016608, 08/28/2015</td>
<td>Carbamazepine</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Boxed Warning, Warnings, Precautions</td>
<td>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>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION

Dihydropyrimidine Dihydrogenase Deficiency

Patients should be advised to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity they are at an increased risk of acute early onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity) [see Warnings and Precautions (5.4)].

BOXED WARNING

Serious dermatologic reactions and HLA-B*1502 allele

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

WARNINGS

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with Tegretol treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Tegretol should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

SJS/TEN and HLA-B*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*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*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*1502, averaging 2% to 4%, but higher in some groups. HLA-B*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). Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*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*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*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*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.

PRECAUTIONS

Laboratory Tests

For genetically at-risk patients (see WARNINGS), high-resolution ‘HLA-B*1502 typing’ is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

WARNINGS

Hypersensitivity Reactions and HLA-A*3101 Allele

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*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS/Multiorgan hypersensitivity below).

HLA-A*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.

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| 022562, 08/08/2013                     | Carglumic Acid | Inborn Errors of Metabolism | NAGS | Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies | 1 INDICATIONS AND USAGE
1.1 Acute hyperammonemia in patients with NAGS deficiency
Carbaglu is indicated as an adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During acute hyperammonemic episodes concomitant administration of Carbaglu with other ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction are recommended.

1.2 Maintenance therapy for chronic hyperammonemia in patients with NAGS deficiency
Carbaglu is indicated for maintenance therapy in pediatric and adult patients for chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be reduced or discontinued based on plasma ammonia levels.

5 WARNINGS AND PRECAUTIONS
5.1 Hyperammonemia
(…) Management of hyperammonemia due to NAGS deficiency should be done in coordination with medical personnel experienced in metabolic disorders. Ongoing monitoring of plasma ammonia levels, neurological status, laboratory tests and clinical responses in patients receiving Carbaglu is crucial to assess patient response to treatment.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
There are no adequate and well controlled studies or available human data with Carbaglu in pregnant women. Decreased survival and growth occurred in offspring born to animals that received carglumic acid at doses similar to the maximum recommended starting human dose during pregnancy and lactation. Because untreated N-acetylglutamate synthase (NAGS) deficiency results in irreversible neurologic damage and death, women with NAGS deficiency must remain on treatment throughout pregnancy. (…) 8.3 Nursing Mothers
It is not known whether Carbaglu is excreted in human milk. Carglumic acid is excreted in rat milk, and an increase in mortality and impairment of body weight gain occurred in neonatal rats nursed by mothers receiving carglumic acid. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Carbaglu, human milk-feeding is not recommended. Treatment is continuous and lifelong for NAGS deficiency patients.

8.4 Pediatric Use
The efficacy of Carbaglu in 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 Carbaglu treatment during infancy or childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Carbaglu, however, data are limited.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
In a retrospective review of the clinical course in 23 patients with NAGS deficiency, carglumic acid reduced plasma ammonia levels within 24 hours when administered with and without concomitant ammonia lowering therapies. No dose response relationship has been identified. (…) 14 CLINICAL STUDIES
14.1 Responses of Patients with NAGS Deficiency to Acute and Chronic Treatment
The efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who received Carbaglu treatment for a median of 7.9 years (range 0.6 to 20.8 years). (See Table 2) (…) Of the 23 NAGS deficiency patients who received Carbaglu treatment for a median of 7.9 years (range 0.6 to 20.8 years). (See Table 2) (…) The mean plasma ammonia level at baseline and the decline that is observed after treatment with Carbaglu in 13 evaluable patients with NAGS deficiency is illustrated in Figure 1. (See Figure 1)

| 204370, 11/09/2017 | Cariprazine | Psychiatry | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
CYP2D6 Poor Metabolizers
CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

Drug Interaction Studies
CYP2D6 inhibitors
CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.

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| 017172, 02/01/2013 | Carisoprodol | Rheumatology | CYP2C19 | Use in Specific Populations, Clinical Pharmacology | 8 USE IN SPECIFIC POPULATION
8.8 Patients with Reduced CYP2C19 Activity
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)]. |

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics

Metabolism
The major pathway of carisoprodol metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism (see Patients with Reduced CYP2C19 Activity below). Patients with Reduced CYP2C19 Activity SOMA should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carisoprodol, and concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.

7 DRUG INTERACTIONS
7.1 CYP2D6 Inhibitors and Poor Metabolizers
Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol [see Clinical Pharmacology (12.3)]. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasoconstricting effects of the higher concentrations of the α-blocking R(+) enantiomer.

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared with extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+) carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephentoin (patients deficient in cytochrome P450 2C19).

| 020067, 10/02/2015 | Carvedilol | Cardiology | CYP2D6 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS
7.1 CYP2D6 Inhibitors and Poor Metabolizers
In patients who are known or suspected to be poor CYP2D6 metabolizers (i.e., CYP2D6*3/*3), based on genotype or previous history/experience with other CYP2D6 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 CYP2D6 metabolizers, consider using alternative treatments. [see Use in Specific Populations (8.4), and Clinical Pharmacology (12.3)]. |

2 DOSAGE AND ADMINISTRATION
2.7 Special Populations
Poor Metabolizers of CYP2C9 Substrates
In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific Populations (8.8), and Clinical Pharmacology (12.5)].

2 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*3/*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*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.9)].

| 020998, 05/08/2016 | Celecoxib | Rheumatology | CYP2C9 | Dosage and Administration, Use in Specific Populations, Clinical Pharmacology | 2 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*3/*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*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.9)].

| 205755, 05/26/2017 | Ceritinib | Oncology | ALK | Indications and Usage, Dosage and Administration, Adverse | 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

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<td>Reactions, Clinical Studies</td>
<td>2.1 Patient Selection</td>
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<td>Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a></td>
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<td>6 ADVERSE REACTIONS</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the Warnings and Precautions section reflect exposure to ZYKADIA 750 mg once daily in 925 patients with ALK-positive NSCLC across seven clinical studies, including ASCEND-4 and ASCEND-1, described below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies. (…)</td>
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<td>The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study of 376 previously untreated ALK-positive NSCLC patients. Patients received ZYKADIA 750 mg daily (N=189) or chemotherapy plus maintenance chemotherapy (N=187). (…)</td>
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<td>The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in ASCEND-1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily). (See Tables 5 and 6) (…)</td>
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<td>The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ASCEND-4, NCT01828099). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. (…)</td>
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<td>14.2 Previously Treated ALK-Positive Metastatic NSCLC</td>
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<td>The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (ASCEND-1, NCT01283516). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily. (…)</td>
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<td>8 USE IN SPECIFIC POPULATIONS</td>
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<td>8.4 Pediatric Use</td>
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<td>Safety and effectiveness of Brineura have been established in pediatric patients 3 years of age and older. Pediatric use of Brineura to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptide 1 (TPP1) deficiency.</td>
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<td>Cetuximab (2)</td>
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<td>RAS</td>
<td>Warnings and Precautions, Adverse Reactions, Clinical Studies</td>
<td>in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment, in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. [See Warnings and Precautions (5.7), Clinical Pharmacology (12.1), Clinical Studies (14.2)]. Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when he results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)].</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Colorectal Cancer
Study 4: EU-Approved Cetuximab in Combination with FOLFIIRI
(…) Table 4 contains selected adverse reactions in 667 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer receiving EU-approved cetuximab plus FOLFIIRI or FOLFIIRI 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)]. Baseline characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population [see Warnings and Precautions (6.7)] (…) Results of the planned PFS and ORR analysis in all randomized patients and post-hoc PFS and ORR analysis in subgroups of patients defined by K-Ras mutation status, and post-hoc analysis of updated OS based on additional follow-up (1000 events) in all randomized patients and in subgroups of patients defined by K-Ras mutation status are presented in Table 8 and Figure 5. The treatment effect in the all randomized population for PFS was driven by treatment effects limited to patients who have K-Ras wild-type tumors. There is no evidence of effectiveness in the subgroup of patients with K-Ras mutant tumors. (See Table 8 and Figure 2) (…) K-Ras status was available for 453/572 (79%) of the patients: 245 (54%) patients had K-Ras wild-type tumors and 208 (46%) 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)]. (See Table 9 and Figure 3) (…) Study 6 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. (…)†

80989, 12/08/2006
Cevimeline Dental CYP2D6 Precautions
(…) Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an in vitro study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline. (…)§

006002, 11/06/2013
Chloroquine Infectious Diseases G6PD 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.

011641, 02/01/2011
Chlorpropamide Endocrinology G6PD Precautions
Hematological Anemia
Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonlurea agents can lead to hemolytic anemia. Because DIABINESE belongs to the class of sulfonlurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonlurea alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

018057, 02/22/2015
Cisplatin Oncology TPMT Adverse Reactions
Otolotoxicity
(…) Genetic factors (e.g., variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.

028822, 01/04/2017
Citalopram (1) Psychiatry CYP2C19 Dosage and Administration, Warnings, Clinical Pharmacology
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)

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**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. Citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGs and DOSAGE AND ADMINISTRATION).

In CYP2C19 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.

**CLINICAL PHARMACOLOGY**

**Population Subgroups**

CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.

**CYP2D6 poor metabolizers**

Coadministration 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.

**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

Concentrations of citalopram’s active metabolite, N-desmethylcitalopram, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended (see Dosage and Administration (2.5), Clinical Pharmacology (12.3)).

**8 USE IN SPECIFIC POPULATIONS**

**8.6 CYP2C19 Poor Metabolizers**

Concentrations of citalopram’s active metabolite, N-desmethylcitalopram, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended (see Dosage and Administration (2.5), Clinical Pharmacology (12.3)).

**12 CLINICAL PHARMACOLOGY**

**12.3 Pharmacokinetics**

Metabolism and Excretion

(…) The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethylcitalopram (see Clinical Pharmacology (12.5)). In CYP2C19 poor metabolizers, levels of N-desmethylcitalopram were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.

**12.5 Pharmacogenomics**

The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethylcitalopram. Compared to CYP2C19 extensive metabolizers, N-desmethylcitalopram AUC and Cmax are approximately 3-5 times higher in poor metabolizers (e.g., subjects with *2/*2 genotype) and 2 times higher in intermediate metabolizers (e.g., subjects with *1/*2 genotype). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted (see Dosage and Administration (2.5)).

The systemic exposure of citalopram is similar for both CYP2C19 poor and extensive metabolizers.

**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).

**BOXED WARNING**

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

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 (see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)). Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed CYP2C19 poor metabolizers). Tests are available to identify patients who are CYP2C19 poor metabolizers (see Clinical Pharmacology (12.5)). Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

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<td>CYP2D6</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers It may be necessary to reduce the CLOZARIL dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)].</td>
</tr>
<tr>
<td>200192, 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>
</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>BOXED WARNING WARNING: ADDICTION, ABUSE, AND MISUSE; LIFETHREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS Death Related to Ultra-Rapid Metabolism of Codeine to Morphine Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism [see Warnings and Precautions (5.3)].</td>
</tr>
</tbody>
</table>

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<th>Biomarker†</th>
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<th>Labeling Text‡</th>
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<tr>
<td></td>
<td></td>
<td>Oncology</td>
<td>ALK</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Pharmacology, Clinical Pharmacology, and Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 ALK-Positive Metastatic NSCLC</td>
<td>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)].</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>2 DOSE AND ADMINISTRATION</td>
<td>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)].</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.1 Patient Selection</td>
<td>Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at <a href="http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm">http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm</a>. 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.</td>
</tr>
<tr>
<td>202570, 01/24/2017</td>
<td>Crizotinib (1)</td>
<td></td>
<td></td>
<td>6 ADVERSE REACTIONS</td>
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<td>202806, 06/22/2017</td>
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<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
<td>RAS1-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.</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. 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, ECOG performance status of 0, 1, or 2, adequate organ function, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRIR and investigator, with imaging performed every 8 weeks for the first 60 weeks. Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (86%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. (See Table 9) |

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<thead>
<tr>
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<td>202806</td>
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#### Clinical Pharmacology

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<tr>
<th>12 CLINICAL PHARMACOLOGY</th>
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</thead>
<tbody>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
</tbody>
</table>

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).

#### Clinical Studies

<table>
<thead>
<tr>
<th>14 CLINICAL STUDIES</th>
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</thead>
<tbody>
<tr>
<td>14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent</td>
</tr>
</tbody>
</table>

In the BREAK-3 study (NCT01227889), the safety and efficacy of TAFINLAR as a single agent were demonstrated in an international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. (…) All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were retrospectively, using an FDA-approved companion diagnostic test, TH4i™-BRAF assay. (…) In supportive analyses based on IRRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the TH4i™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis. The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multicenter trial. (See Table 10) (…)

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

The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908). 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 with 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 ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases. (See Table 11 and Figures 1, 2, 3)

| 14.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC) |

In Study BRF113928 (NCT01338634), 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 for TAFINLAR 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). (…)

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<tr>
<td>202806, 06/23/2017</td>
<td>Dabrafenib (2)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Warnings and</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Adverse Reactions, Patient Counseling Information</td>
<td>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.</td>
</tr>
<tr>
<td>2020843, 06/22/2017</td>
<td>Daclatasvir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<tr>
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<td></td>
<td>14.2 Clinical Trials in HCV Genotype 3 (ALLY-3)</td>
</tr>
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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 NSSA amino acid polymorphisms, see Microbiology (12.4). (…)</td>
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<tr>
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<td></td>
<td>14.3 Clinical Trials in HCV/HIV Coinfected Subjects (ALLY-2)</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. (…)</td>
</tr>
<tr>
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<td>14.4 Clinical Trials in Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Recurrence after Liver Transplantation (ALLY-1)</td>
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<tr>
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<td>(...) Fifty-eight percent of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 1% had genotype 2, 3% had genotype 3, 4% had genotype 4, and 1% had genotype 6, 7% had IL28B rs12979860 non-CC genotype. (…)</td>
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<td>Dapsone (1)</td>
<td>Dermatology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Use in Specific Populations</td>
<td>5 WARNINGS AND PRECAUTIONS 5.2 Hematologic Effects Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry. Some subjects with G6PD deficiency using ACZONE® Gel developed laboratory changes suggestive of hemolysis. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel, 5%, 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 haptoglobin or lactate dehydrogenase during ACZONE® or vehicle treatment at either the 2-week or 12-week time point. The proportion of subjects who experienced decreases in hemoglobin ≥1 g/dL was similar between ACZONE® Gel, 5% and vehicle treatment (8 of 58 subjects had such decreases during ACZONE® treatment compared to 7 of 56 subjects during vehicle treatment 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.</td>
</tr>
<tr>
<td>021794, 07/08/2015</td>
<td>Dapsone (2)</td>
<td>Dermatology</td>
<td>Nonspecific (Congenital or Inherited) Methemoglobinemia</td>
<td>Warnings and Precautions</td>
<td>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.</td>
</tr>
<tr>
<td>086841</td>
<td>Dapsone (3)</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions, Overdosage</td>
<td>Labeling not electronically available on Drugs@FDA</td>
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<tr>
<td>021513, 03/15/2012</td>
<td>Darifenacin</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics Electrocardiography The effect of six-day treatment of 15 mg and 75 mg Enablex on QTcF 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 QTcF interval prolongation at any time during the steady-state, while moxifloxacin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the clinical efficacy and safety studies, the change in 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. Variability in Metabolism</td>
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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.

Drug-Drug Interactions
CYP3A4 Inhibitors
In a drug interaction study, when a 7.5 mg once daily dose of Enablex was given 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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<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text†</th>
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</thead>
<tbody>
<tr>
<td>Diftitox 103767, 08/30/2011</td>
<td></td>
<td>Oncology</td>
<td>IL2RA (CD25 antigen)</td>
<td>Indications and Usage, Warnings and Precautions, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>5 WARNINGS AND PRECAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Myelosuppression:</td>
</tr>
<tr>
<td>Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML. In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated. (…)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.2 Bleeding-Related Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction in vitro. In all CML or Ph+ ALL clinical studies, grade 3 central nervous system (CNS) hemorrhages, including fatalities, occurred in &lt;1% of patients receiving SPRYCEL. Grade 3 or greater gastrointestinal hemorrhage, including fatalities, occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of grade 3 hemorrhage occurred in 2% of patients. Most bleeding events in clinical studies were associated with severe thrombocytopenia. Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.3 Fluid Retention</th>
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</thead>
<tbody>
<tr>
<td>(…) In patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural effusion reported in 7% of patients. (…)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6 ADVERSE REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(…) The data described below reflect exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and in 2388 patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2712 SPRYCEL-treated patients was 19.2 months (range 0–93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1618 patients with chronic phase CML was 29 months (range 0–92.9 months). The median duration of therapy in 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months). (…) In the randomized trial in patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 39%. Among the 1818 SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation were reported in 329 (20.3%) patients; among the 1094 SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, drug-related adverse events leading to discontinuation were reported in 191 (17.5%) patients. (…)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6.2 Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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. (…)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6.3 Additional Pooled Data From Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following additional adverse reactions were reported in patients in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–&lt;10%, 0.1%–&lt;1%, or &lt;0.1%. These events are included on the basis of clinical relevance.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>14 CLINICAL STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>(…) BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L, and V299L. Dasatinib does not appear to be active against the T315I mutation, based on in vitro data.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months); or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. (…) The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 60%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MHR), defined as either a CHR or no evidence of leukemia (NEL). Advanced Phase CML and Ph+ ALL. Dose-Optimization Trial: One randomized open-label trial was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. (See Table 12) (…) In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MHR was 4.6 months (min-max: 1.4–10.2). The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twicedaily were 4.0 months (min-max: 0.4–11.0) and 3.1 months (min-max: 0.3–20.8), respectively.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>1 INDICATIONS AND USAGE</th>
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<tbody>
<tr>
<td>Ontak is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the II-2 receptor (see Warnings and Precautions (5.4)).</td>
</tr>
</tbody>
</table>

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<tr>
<td><strong>014399, 07/02/2014</strong></td>
<td>Desipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>5.4 CD25 Tumor Expression and Evaluation</td>
</tr>
<tr>
<td><strong>021118, 11/04/2016</strong></td>
<td>Desflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td><strong>021802, 12/16/2017</strong></td>
<td>Desvenlafaxine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td><strong>208082, 04/03/2017</strong></td>
<td>Deutetrabenazine</td>
<td>Neurology</td>
<td>CYP2D6</td>
<td>Dosage and Administration</td>
<td>2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers</td>
</tr>
<tr>
<td><strong>022287, 10/24/2016</strong></td>
<td>Dextansoprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
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<td>Contraindications</td>
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**5 WARNINGS AND PRECAUTIONS**

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<td>Contraindications</td>
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</table>

**5.4 CD25 Tumor Expression and Evaluation**

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

**14 CLINICAL STUDIES**

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</table>

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

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

**14.2 Study 2: Dose Evaluation Study in CTCL (Stage Iib to Iva) Patients**

A randomized, double-blind study was conducted to evaluate doses of 9 or 18 mcg/kg/day in 71 patients with recurrent or persistent, Stage Iib to Iva CTCL. Entry to this study required demonstration of CD25 expression on at least 20% of the cells in any relevant tumor tissue sample (skin biopsy) or circulating cells. Tumor biopsies were not evaluated for expression of other IL-2 receptor subunit components (CD22/CD132).

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</table>
| 021879, 01/20/2015                      | Dextromethorphan and Quinidine | Neurology | CYP2D6 | Warnings and Precautions, Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Metabolism
(...) CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates: extensive metabolizers (*/*1), intermediate metabolizers (*1/1mutant), and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.
Cytochrome P 450 Interactions
(...) Although in vitro studies indicated that DEXILANT has the potential to inhibit CYP2C19 in vivo, an in vivo drug-drug interaction study in mainly CYP2C19 extensive and intermediate metabolizers has shown that DEXILANT does not affect the pharmacokinetics of diazepam (CYP2C19 substrate).
(...) Clopidogrel
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with DEXILANT 60 mg capsules (n=40), for nine days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 86-97%) when DEXILANT was 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 mcM ADP) was related to the change in exposure to clopidogrel active metabolite. The effect on exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important.
12.5 Pharmacogenomics
Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole
Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of DEXILANT 30 mg or 60 mg capsules (N=2 to 6 subjects/group), mean dexlansoprazole Cmax and AUC values were up to two times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean Cmax was up to four times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.
5 WARNINGS AND PRECAUTIONS
5.4 Concomitant use of CYP2D6 Substrates
The quinidine in NUDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited (see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)). Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUDEXTA that are metabolized by CYP2D6 (see Drug Interactions (7.5)).
5.8 CYP2D6 Poor Metabolizers
The quinidine component of NUDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone (see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3), (12.5)). Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of NUDEXTA is not expected to contribute to the effectiveness of NUDEXTA 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 NUDEXTA.

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<tr>
<td>020848, 12/16/2016</td>
<td>Diazepam</td>
<td>Neurology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination (…) The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-6% of Caucasians have little or no activity and are “poor metabolizers”) and CYP3A4. (…)</td>
</tr>
<tr>
<td>125516, 03/10/2015</td>
<td>Dinutuximab</td>
<td>Oncology</td>
<td>MYCN</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES (…) Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. (…)</td>
</tr>
<tr>
<td>204760, 06/09/2016</td>
<td>Dolutegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).</td>
</tr>
<tr>
<td>020236, 03/17/2010</td>
<td>Doxepin (1)</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Special Population Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
<tr>
<td>020236, 03/17/2010</td>
<td>Doxepin (2)</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.5 Special Population Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
<tr>
<td>205525, 07/01/2016</td>
<td>Dronabinol</td>
<td>Gastroenterology</td>
<td>CYP2C9</td>
<td>Use in Specific Populations, Clinical Pharmacology</td>
<td>8 USE IN SPECIFIC POPULATIONS 8.6 Effect of CYP2C9 Polymorphism Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function (see Clinical Pharmacology (12.5)).</td>
</tr>
<tr>
<td>021876, 06/01/2015</td>
<td>Drospirenone and Ethinyl Estradiol</td>
<td>Gynecology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Effects of Combined Oral Contraceptives on Other Drugs (…) In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 (genotype) the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. (…)</td>
</tr>
<tr>
<td>021427, 01/04/2017</td>
<td>Duloxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS 7.3 Dual Inhibition of CYP1A2 and CYP2D6 Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.</td>
</tr>
<tr>
<td>761069, 02/16/2018</td>
<td>Durvalumab</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Specific Populations Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance [CLcr] 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status was unknown or missing in 19% of patients. (…)</td>
</tr>
<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 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype</td>
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following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6*1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see Warnings and Precautions (5.2)).

### 14.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE COINFEC)

(...)

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 1:1.1:1 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); 76% of the subjects were male; 72% were White; 20% were Black or African American; 8% were Hispanic or Latino; mean body mass index was 26 kg/m²; 44% had baseline HCV RNA levels greater than 800,000 IU/mL; 71% 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 COINFEC was an open-label, single-arm trial in treatment-naïve HCV/HIV-1 co-infected 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; 61% had cirrhosis; 80% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (...)

### 14.3 Clinical Trials in Treatment-Experienced Subjects with Genotype 1 HCV (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 treatment with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1:1 ratio to one of the following treatment groups: ZEPATIER for 12 weeks, ZEPATIER + RBV for 12 weeks, ZEPATIER for 16 weeks, or ZEPATIER + RBV for 16 weeks. Among subjects with genotype 1 infection, the median age was 57 years (range: 19 to 77); 64% of the subjects were male; 67% were White; 18% were Black or African American; 9% were Hispanic or Latino; mean body mass index was 28 kg/m²; 78% had baseline HCV RNA levels greater than 800,000 IU/mL; 70% had cirrhosis; 79% had non-C/C IL28B alleles (CT or TT); and 60% had genotype 1a, 39% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (...)

C-EDGE TE was a randomized, open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simprevir, or telaprevir in combination with PegIFN + RBV. Subjects received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects had a median age of 55 years (range: 23 to 75); 58% of the subjects were male; 74% were White; 3% were Black or African American; 15% were Hispanic or Latino; mean body mass index was 28 kg/m²; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; and 46% had non-C/C IL28B alleles (CT or TT); 46% had baseline NS3 resistance-associated substitutions.

Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were well consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions (see Microbiology) (12.4).

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

C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m²) or CKD Stage 5 (eGFR<15 mL/min/1.73 m²), including subjects on hemodialysis, who were treated with PegIFN + RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 97% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; 50% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (...)

### 14.5 Clinical Trial in Subjects with Genotype 1 HCV and Chronic Hepatitis C (C-EDGE CER)

C-EDGE CER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic HCV infection. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; 72% had non-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.

### 14.6 Clinical Trial in Subjects with Genotype 1 HCV and Treatment-Experienced Subjects with fibroScan ≥ 8 kPa (C-EDGE FE)

C-EDGE FE was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior treatment with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1:1 ratio to one of the following treatment groups: EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 97% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; 50% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (...)

### 14.7 Clinical Trial in Subjects with Genotype 1 HCV and Fibrosis <2 kPa (C-EDGE FF)

C-EDGE FF was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic HCV infection. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 97% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; 72% had non-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.

### 14.8 Clinical Trial in Subjects with Genotype 1 HCV and Fibrosis 2 kPa <8 kPa (C-EDGE F)

C-EDGE F was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic HCV infection. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; 72% had non-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.

### 14.9 Clinical Trial in Subjects with Genotype 1 HCV and Fibrosis 8 kPa <10 kPa (C-EDGE F)

C-EDGE F was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic HCV infection. Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; 72% had non-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.
### Table of Pharmacogenomic Biomarkers in Drug Labeling

**Last Updated: 06/2018**

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

<table>
<thead>
<tr>
<th><strong>2.2 Recommended Adult Dosage</strong></th>
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</thead>
<tbody>
<tr>
<td>The recommended dosage of CERDELGA is 84 mg twice daily in CYP2D6 EMs and IMs. The recommended dosage in CYP2D6 PMs is 84 mg once daily.</td>
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<tr>
<td>The predicted exposures with 84 mg once daily in patients who are CYP2D6 PMs are expected to be similar to exposures observed with 84 mg twice daily in CYP2D6 IMs [see Clinical Pharmacology (12.3)].</td>
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<tr>
<td>Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient’s metabolizer status [see Contraindications (4)].</td>
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<table>
<thead>
<tr>
<th><strong>4 CONTRAINDICATIONS</strong></th>
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<tbody>
<tr>
<td>CERDELGA is contraindicated in the following patients due to the risk of significantly increased eliglustat plasma concentrations which may result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias.</td>
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<td><strong>EMs or IMs taking a strong or moderate CYP2D6 inhibitor.</strong></td>
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<tr>
<td><strong>PMs or PMs taking a strong CYP3A inhibitor.</strong></td>
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<table>
<thead>
<tr>
<th><strong>5 WARNINGS AND PRECAUTIONS</strong></th>
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<tr>
<td><strong>5.1 Drug-Drug Interactions</strong></td>
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<thead>
<tr>
<th><strong>7 DRUG INTERACTIONS</strong></th>
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<tbody>
<tr>
<td><strong>7.1 Potential for Other Drugs to Affect CERDELGA</strong></td>
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<table>
<thead>
<tr>
<th><strong>12 CLINICAL PHARMACOLOGY</strong></th>
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<tbody>
<tr>
<td><strong>12.3 Pharmacokinetics</strong></td>
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<tr>
<td>At a given dose, the systemic exposure (Cmax and AUC) depends on the CYP2D6 phenotype.</td>
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<tr>
<td>In CYP2D6 EMs and IMs, the eliglustat pharmacokinetics are time-dependent and the systemic exposure increases in a more than dose proportional manner.</td>
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<tr>
<td>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 (AUC0–12).</td>
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<td>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- to 9-fold higher in PMs.</td>
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<table>
<thead>
<tr>
<th><strong>Absorption</strong></th>
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<tbody>
<tr>
<td>In CYP2D6 EMs, median time to reach maximum plasma concentrations (tmax) occurs at 1.5 to 2 hours following multiple doses of CERDELGA 84 mg twice daily.</td>
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<tr>
<td>The corresponding mean Cmax values range from 12.1 to 25.0 ng/mL in EMs. The mean AUC(t) values range from 76.3 to 143 hr*ng/mL in EMs.</td>
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<tr>
<td>The Cmax and AUC(t) in one IM subject receiving multiple doses of CERDELGA 84 mg twice daily was 44.6 ng/mL and 306 hr*ng/mL, respectively.</td>
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<tr>
<th><strong>Absorption</strong></th>
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<tr>
<td>The mean AUC(t) values range from 76.3 to 143 hr*ng/mL in EMs.</td>
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<tr>
<td>The Cmax and AUC(t) in one IM subject receiving multiple doses of CERDELGA 84 mg twice daily was 44.6 ng/mL and 306 hr*ng/mL, respectively.</td>
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<tr>
<th><strong>Distribution</strong></th>
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<tbody>
<tr>
<td>Eliglustat is moderately bound to human plasma proteins (76 to 83%).</td>
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<tr>
<td>In the blood, it is mainly distributed in plasma and not red blood cells.</td>
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<td>After intravenous (IV) administration, the volume of distribution of eliglustat was 835 L in CYP2D6 EMs, suggesting wide distribution to tissues (CERDELGA is only for oral use).</td>
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<thead>
<tr>
<th><strong>Metabolism and Elimination</strong></th>
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<tbody>
<tr>
<td>After oral administration of 84 mg [14 280 C]-eliglustat, the majority of the administered dose is excreted in urine (41.8%) and feces (51.4%), mainly as metabolites.</td>
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<tr>
<td>After 42 mg IV administration in healthy volunteers, mean (CV%) of eliglustat total body clearance was 88 L/h (8.8%) in CYP2D6 EMs (CERDELGA is only for oral use).</td>
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| **Biomarkers do not necessarily reflect the terminology used in labeling.** | | | | |
| The term “Nonspecific” is provided when labeling does not explicitly identify the specific biomarker(s) or when the biomarker is represented by a molecular phenotype or gene signature, and in some cases the biomarker was inferred based on the labeling language. | | | | |

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

Last Updated: 06/2018

<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>125460, 02/14/2014</td>
<td>Elosulfase</td>
<td>Inborn Errors of Metabolism</td>
<td>GALNS</td>
<td>Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td><strong>Vimizim (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).</strong></td>
</tr>
</tbody>
</table>

### Drug Interactions - Effect of Other Drugs on CERDELGA

In vitro, eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A4. Eliglustat is also a substrate of P-glycoprotein (P-gp).

Co-administration of CERDELGA with CYP2D6 Inhibitors

Systemic exposure (Cmax and AUC) of eliglustat increased 7.0-fold and 8.4-fold, respectively, following co-administration of CERDELGA 84 mg twice daily with paroxetine (a strong CYP2D6 inhibitor) 30 mg once daily in EMs (N=33), respectively. Simulations using PBPK models suggested that paroxetine may increase the Cmax and AUC of eliglustat 2.1- and 2.3-fold in IMs, respectively.

Compared to paroxetine, the effects of terbinafine (a moderate inhibitor of CYP2D6) on the exposure of eliglustat in EMs or IMs were predicted to be smaller. Simulations using PBPK models suggested that terbinafine may increase the Cmax and AUC of eliglustat 3.8- and 4.5-fold in EMs, respectively.

Both Cmax and AUC of eliglustat increased 1.6-fold in IMs.

Co-administration of CERDELGA with CYP3A Inhibitors

CYP2D6 EMs and IMs: Following co-administration of CERDELGA 84 mg twice daily with ketoconazole (a strong CYP3A inhibitor) 400 mg once daily, the systemic exposure (Cmax and AUC) of eliglustat increased 4.0-fold and 4.4-fold in EMs (N=31).

Simulations using PBPK models suggested that ketoconazole may increase the Cmax and AUC of eliglustat 4.4- and 5.4-fold, respectively. Compared to ketoconazole, the effects of fluconazole (a moderate inhibitor of CYP3A) on the exposure of eliglustat in EMs or IMs were predicted to be smaller. Simulations using PBPK models suggested that fluconazole may increase the Cmax and AUC of eliglustat 2.8- and 3.2-fold in EMs, respectively, and 2.5- to 2.9-fold in IMs, respectively.

CYP2D6 PMs:

The effect of CYP3A inhibitors on the systemic exposure of eliglustat in PMs has not been evaluated in clinical studies. Simulations using PBPK models suggest that ketoconazole may increase the Cmax and AUC of eliglustat 4.3- and 6.2-fold when co-administered with CERDELGA 84 mg once daily in PMs. Simulations using PBPK models suggest that fluconazole may increase the Cmax and AUC of eliglustat 2.4- and 3.0-fold, respectively, when co-administered with CERDELGA 84 mg once daily.

Co-administration of CERDELGA with CYP2D6 and CYP3A Inhibitors

Simulations using PBPK models suggested that co-concomitant use of CERDELGA 84 mg twice daily with paroxetine and ketoconazole may increase the Cmax and AUC of eliglustat 10.2- and 13.6-fold in EMs, respectively. The predicted Cmax and AUC of eliglustat increased 7.5- to 9.8-fold in IMs, respectively.

Simulations using PBPK models suggested that concomitant use of CERDELGA 84 mg twice daily with terbinafine and ketoconazole may increase the Cmax and AUC of eliglustat 16.7- and 24.2-fold in EMs, respectively. The predicted Cmax and AUC of eliglustat increased 4.2- to 5.0-fold in IMs, respectively.

**Effect of CYP3A Inducers on Eliglustat PK**

Systemic exposures (Cmax and AUC) of eliglustat decreased by approximately 90% in EMs and IMs following co-administration of CERDELGA 127 mg twice daily with rifampin (a strong CYP3A inducer) 600 mg PO once daily. The only approved dose of CERDELGA is 84 mg. Systemic exposures of eliglustat decreased by approximately 95% following co-administration of CERDELGA 84 mg twice daily with rifampin 600 mg PO once daily in PMs.

**Effect of OATP (organic anion transporting polypeptide) Inhibitors on Eliglustat PK**

Systemic exposures of eliglustat were similar with or without co-administration of single 600 mg IV dose of rifampin (a potent OATP inhibitor) regardless of subjects’ CYP2D6 phenotypes.

Drug Interactions - Effect of CERDELGA on the PK of Other Drugs

Eliglustat is an inhibitor of P-gp and CYP2D6.

Following multiple doses of CERDELGA 127 mg twice daily, systemic exposures (Cmax and AUC) to metoprolol (a CYP2D6 substrate) increased compared to metoprolol administration alone. Mean Cmax and AUC increased by 1.7- and 2.3-fold, respectively, in EMs and by 1.2- and 1.6-fold, respectively, in IMs. The only approved dose of CERDELGA is 84 mg.

Following multiple doses of CERDELGA 127 mg twice daily in EMs and IMs or 84 mg twice daily in PMs, systemic exposures (Cmax and AUC) to digoxin (a P-gp substrate, with narrow therapeutic index) increased compared to digoxin administration alone. Mean Cmax and AUC increased by 1.7- and 1.5-fold, respectively. The only approved dose of CERDELGA is 84 mg.

### 14 CLINICAL STUDIES

(…) The CERDELGA treatment group was comprised of IM (5%), EM (90%) and URM (5%) patients. (…)

### 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...
### Table of Pharmacogenomic Biomarkers in Drug Labeling
**Last Updated: 06/2018**

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<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Therapeutic Area*</th>
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<th>Labeling Sections</th>
<th>Labeling Text†</th>
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<td>022291, 10/12/2016</td>
<td>Eltrombopag (1)</td>
<td>Hematology</td>
<td>F5 (Factor V Leiden)</td>
<td>Warnings and Precautions</td>
<td>5 <strong>WARNINGS AND PRECAUTIONS</strong>&lt;br&gt;5.3 Thrombotic/Thromboembolic Complications&lt;br&gt;The pharmacokinetics of eltrombopag 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. (…)</td>
</tr>
<tr>
<td>022291, 10/12/2016</td>
<td>Eltrombopag (2)</td>
<td>Hematology</td>
<td>SERPINC1 (Antithrombin III)</td>
<td>Warnings and Precautions</td>
<td>5 <strong>WARNINGS AND PRECAUTIONS</strong>&lt;br&gt;5.3 Thrombotic/Thromboembolic Complications&lt;br&gt;The pharmacokinetics of eltrombopag 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. (…)</td>
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<tr>
<td>209606, 08/01/2017</td>
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<td>Oncology</td>
<td>IDH2</td>
<td>Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies</td>
<td>1 <strong>INDICATIONS AND USAGE</strong>&lt;br&gt;1.1 Acute Myeloid Leukemia&lt;br&gt;IDHIFA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.</td>
</tr>
</tbody>
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<tr>
<td>210496, 06/27/2018</td>
<td>Encorafenib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>BRAF TOVI™ 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: BRAF TOVI is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].</td>
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<tr>
<td>017087, 01/21/2010</td>
<td>Enflurane</td>
<td>Anesthesiology</td>
<td>Non-specific (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>021743, 10/18/2016</td>
<td>Erlotinib</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Indications and Usage</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>12/20/2016</td>
<td>022101, 01/04/2017 021323, 01/04/2017 062759</td>
<td>Esomeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions</td>
<td>7 DRUG INTERACTIONS</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>7.3 Effects on Hepatic Metabolism/Cytochrome P450 Pathways</td>
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<td></td>
<td></td>
<td>(…), Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male participants, the maximum recommended therapeutic dose at steady state was 20 mg. The exposure under supratherapeutic 40 mg is similar to the steady state concentration expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.</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>EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see Clinical Studies (14)]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.</td>
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<td>022334, 06/14/2016</td>
<td>Everolimus (1)</td>
<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Studies</td>
<td>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.</td>
</tr>
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| 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 | 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. (…) |

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</table>
| 020763, 06/18/2018                     | Exemestane | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Dosage and Administration, Clinical Studies | 1 INDICATIONS AND USAGE  
1.1 Adjuvant Treatment of Postmenopausal Women  
AROMASIN is indicated for adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy [see Clinical Studies (14.1)]. (...) |
| 022030, 11/21/2017                    | Fesoterodine | Urology | CYP2D6 | Drug Interactions, Clinical Pharmacology | 7 DRUG INTERACTIONS  
7.2 CYP3A4 Inhibitors  
Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. Co-administration of the potent CYP3A4 inhibitor ketoconazole with fesoterodine led to approximately a doubling of the maximum concentration (Cmax) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of fesoterodine. Compared with CYP2D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole [see Clinical Pharmacology (12.3), Warnings and Precautions (5.8), and Dosage and Administration (2.1)]. (...)  
7.4 CYP2D6 Inhibitors  
The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors.  
12 CLINICAL PHARMACOLOGY  
12.2 Pharmacodynamics  
Cardiac Electrophysiology  
(...) Electrocardiographic parameters were measured over a 24-hour period at pre-dose, after the first administration, and after the third administration of study medication. Fesoterodine 28 mg was chosen because this dose, when administered to CYP2D6 extensive metabolizers, results in an exposure to the active metabolite that is similar to the exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg together with CYP3A4 blockade. (...)  
12.3 Pharmacokinetics  
Absorption  
(...) A summary of pharmacokinetic parameters for the active metabolite after a single dose of Toviaz 4 mg and 8 mg in extensive and poor metabolizers of CYP2D6 is provided in Table 2. (See Table 2) (...)  
Metabolism  
(...) Variability in CYP2D6 Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6. Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 poor metabolizers, as compared to extensive metabolizers.  
Drug-Drug Interactions  
CYP3A4 Inhibitors: Following blockade of CYP3A4 by co-administration of the potent CYP3A4 inhibitor ketoconazole 200 mg twice a day for 5 days, Cmax and AUC of the active metabolite of fesoterodine increased 2.0- and 2.3-fold, respectively, after oral administration of Toviaz 8 mg to CYP2D6 extensive metabolizers. In CYP2D6 poor metabolizers, Cmax and AUC of the active metabolite of fesoterodine increased 2.1- and 2.5-fold, respectively, during coadministration of ketoconazole 200 mg twice a day for 5 days. Cmax and AUC of the active metabolite of fesoterodine increased 1.5- and 1.9-fold, respectively, in CYP2D6 poor metabolizers. Cmax and AUC were 3.4- and 4.2 fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. In a separate study coadministering fesoterodine with ketoconazole 200 mg once a day for 5 days, the Cmax and AUC values of the active metabolite of fesoterodine were increased 2.2-fold in CYP2D6 extensive metabolizers and 1.5- and 1.9-fold, respectively, in CYP2D6 poor metabolizers. Cmax and AUC were 2.2-fold and 2.4 fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. There is no clinically relevant effect of moderate CYP3A4 inhibitors on the pharmacokinetics of fesoterodine. (...)  
CYP2D6 Inhibitors: The interaction with CYP2D6 inhibitors was not studied. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. (See Drug Interactions 7.4). |

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<td>Flibanserin (1)</td>
<td>Gynecology</td>
<td>CYP2C9</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. CYP2C9 Poor Metabolizers A study comparing fomoteranib exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADYTI and a strong CYP2C9 inhibitor. In 8 women who were poor metabolizers of CYP2C9, Cmax and AUC0-inf of fomoteranib 100 mg once daily decreased 23% and 18%, compared to exposures among 8 extensive metabolizers of CYP2C9.</td>
</tr>
<tr>
<td>022520, 08/18/2015</td>
<td>Flibanserin (2)</td>
<td>Gynecology</td>
<td>CYP2C19</td>
<td>Adverse Reactions, Use in Specific Populations, Clinical Pharmacology</td>
<td>6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Syncope in Poor CYP2C19 Metabolizers In a pharmacogenomic study of 100 mg ADYTI in subjects who were poor or extensive CYP2C19 metabolizers, syncope occurred in 1/9 (11%) subjects who were poor metabolizers (this subject had a 3.2 fold higher fomoteranib exposure compared to CYP2C9 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C19 extensive metabolizers [see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)].</td>
</tr>
<tr>
<td>022520, 08/18/2015</td>
<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. CYP2D6 Poor Metabolizers A study comparing fomoteranib exposure in CYP2D6 poor metabolizers to CYP2D6 extensive metabolizers was conducted in lieu of a drug interaction study with paroxetine, a strong CYP2D6 inhibitor. In 12 poor metabolizers of CYP2D6, steady state Cmax and AUC0-inf of fomoteranib 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>
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<tr>
<td>020885, 12/16/2003</td>
<td>Fluorouracil (1)</td>
<td>Dermatology</td>
<td>DPYD</td>
<td>Contraindications, Warnings</td>
<td>CONTRAINDICATIONS (…) Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catalyzed by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. (…)</td>
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<td>012309, 07/29/2016</td>
<td>Fluorouracil (2)</td>
<td>Oncology</td>
<td>DPYD</td>
<td>Warnings and Precautions,</td>
<td>5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity</td>
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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 at an increased risk for severe early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil.

Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

17 PATIENT COUNSELING INFORMATION

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

CLINICAL PHARMACOLOGY

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

Clinical issues related to metabolism/elimination

Variability in metabolism- A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2C9 (CYP2C9). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled oral fluoxetine, patients 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.

Drug interactions

Drugs metabolized by CYP2D6- Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death 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).

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.

12.3.2 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.

7 DRUG INTERACTIONS

7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes

(…) Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as “poor metabolizers” (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluoroxime, an in vivo study of fluoroxime 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 25%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluoroxime is metabolized, at least in part, by

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<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions, Clinical Pharmacology</td>
<td>PRECAUTIONS</td>
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<td></td>
<td>Drugs interactions</td>
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<td>Oncology</td>
<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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>
</tr>
<tr>
<td>021344, 07/12/2016</td>
<td>Fulvestrant (2)</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
<td>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.</td>
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</table>
| 021169, 02/14/2017                     | Galantamine | Neurology | CYP2D6 | Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics Metabolism and Elimination Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly. O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In studies of oral 3 H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity, 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 Cmax. The Cmax and Tmax of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with Cmax about 25% lower and median Tmax occurring about 4.5–5.0 hours after dosing. Dose-proportionality is observed for RAZADYNE® ER extended-release capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER extended-release capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. (…) CYP2D6 Poor Metabolizers Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% AUC< increase of unchanged galantamine compared to extensive metabolizers. A total of 356 patients with Alzheimer’s disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (m(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 tailored to tolerability. 1 INDICATIONS AND USAGE IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (see Clinical Studies (14)). Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations [see Clinical Studies (14)]. 2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Select patients for the first-line treatment of metastatic NSCLC with IRESSA based on the presence of EGFR exon 19 deletion or exon 21 (L858R) substitution mutations in their tumor (see Indications and Usage (1), Clinical Studies (14)). Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics. 14 CLINICAL STUDIES Non-Small Cell Lung Cancer (NSCLC) Study 1 The efficacy and safety of IRESSA for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or L858R substitution mutations was evaluated in a multicenter, single-arm, open-label clinical study (Study 1). A total of 106 treatment-naive patients with metastatic EGFR mutation positive NSCLC received IRESSA at a dose of 250 mg once daily until disease progression or intolerable toxicity. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by both a Blinded Independent Central Review (BICR) and investigators. Duration of response (DOR) was an additional outcome measure. Eligible patients were required to have a deletion in EGFR exon 19 or L858R, L861Q, or G719X substitution mutation and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. Tumor samples from 87 patients were tested retrospectively using the therscreen®-EGFR RGG PCR Kit. The study population characteristics were: median age 65 years, age 75 years or older (25%), age less than 65 years (49%), white (100%), female (71%), never smokers (64%), WHO PS 0 (45%), WHO PS 1 (48%), WHO PS 2 (7%), and adenocarcinoma histology (97%). Sixty patients had exon 19 deletions (65%), 20 patients had L858R substitution (31%), while two patients each had tumors harboring L861Q or G719X substitution mutation. The median duration of treatment was 8.0 months. (See Table 3) The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation with duration of response of at least 2.8 months and 5.6 months, respectively. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response with duration of response of at least 2.8 months. Study 2 The results of Study 1 were supported by an exploratory analysis of a subset of a randomized, multicenter, open-label trial (Study 2) conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients were randomized (1:1) to receive IRESSA 250 mg orally.  † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. 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<td>206955, 07/13/2015</td>
<td>Gefitinib (2)</td>
<td>Oncology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP2D6 Poor metabolizer:</td>
<td>CYP2D6 metabolizes gefitinib to O-desmethyl gefitinib in vitro. In healthy CYP2D6 poor metabolizers, O-desmethyl gefitinib concentration was not measurable and the mean exposure to gefitinib was 2-fold higher as compared to the extensive metabolizers. This increase in exposure in CYP2D6 poor metabolizers may be clinically important because some adverse drug reactions are related to higher exposure of gefitinib. No dose adjustment is recommended in patients with a known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse reactions. The impact of CYP2D6 inhibiting drugs on gefitinib pharmacokinetics has not been evaluated. However, similar precautions should be used when administering CYP2D6 inhibitors with IRESSA because of the possibility of increased exposure in these patients. An exploratory exposure response analysis showed an increase in the incidence of interstitial lung disease (ILD) with a greater than 2 fold increase in the CYP2D6 Poor metabolizers group.</td>
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<tr>
<td>020496, 12/19/2016</td>
<td>Glyburide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<tr>
<td>017783, 08/18/2016</td>
<td>Glipizide</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>020051, 05/22/2015</td>
<td>Glimepiride</td>
<td>Endocrinology</td>
<td>G6PD</td>
<td>Precautions</td>
<td>PRECAUTIONS</td>
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<td>020727, 04/02/2015</td>
<td>Hydralazine</td>
<td>Cardiology</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
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<tr>
<td>205552, 01/18/2017</td>
<td>Ibrutinib (1)</td>
<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Indications and Usage, Clinical Studies</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>205552, 01/18/2017</td>
<td>Ibrutinib (2)</td>
<td>Oncology</td>
<td>Chromosome 11q</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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Once daily or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and objective response rate (ORR) as assessed by BICR. The subset population consisted of 186 of 1217 patients (15%) determined to be EGFR positive by the same clinical trial assay as used in Study 1 and had radiographic scans available for a retrospective assessment by BICR. In this subset, there were 88 IRESSA-treated patients and 98 carboplatin/paclitaxel-treated patients. (…)
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| 022192, 05/26/2016                    | Iloperidone | Psychiatry | CYP2D6 | Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology | 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%).
   Study 4
   (...). The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor > 5 cm and 26% presented with del11q. |
| 021588, 09/27/2016                    | Imatinib (1) | Oncology | KIT | Indications and Usage, Dosage and Administration, Clinical Studies | Study 3
   1.6 Aggressive Systemic Mastocytosis (ASM)
   Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test [see Dosage and Administration (2.7)] or with c-Kit mutational status unknown.
   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. |

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<td>021568, 09/27/2016</td>
<td><strong>Imatinib (2)</strong></td>
<td><strong>Oncology</strong></td>
<td><strong>BCR-ABL1 (Philadelphia chromosome)</strong></td>
<td><strong>Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</strong></td>
<td>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>
</tr>
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</table>

### 1 INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

### 2 DOSAGE AND ADMINISTRATION

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

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

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

2.2 Pediatric Patients with Ph+ CML CP

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

2.3 Adult Patients with Ph+ ALL

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

2.4 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.

2.4.1 Dose Adjustment for Hematologic Adverse Reactions

### 14 CLINICAL STUDIES

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

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

14.2 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 Abi, Kit or PDGFR protein tyrosine kinases. (…)

14.3 Newly Diagnosed Philadelphia Chromosome Positive Gastrointestinal Stromal Tumors

- A second randomized, multicenter, open-label, phase 2 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 50/50 HPF, or tumors ruptured into the peritoneal cavity. (…)

### 14.4 Dermatofibrosarcoma Protuberans

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

### 14.5 Myelodysplastic/Myltopylloproliferative 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 Abi, Kit or PDGFR protein tyrosine kinases. (…)

### 14.6 Aggressive Systemic Mastocytosis

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

### 14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia

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

### 14.8 Dermatofibrosarcoma Protuberans

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

### 14.9 Gastrointestinal Stromal Tumors

- An open-label, multinational Phase 2 study was conducted in patients with Kit (CD117) positive unresectable or metastatic malignant GIST. (…)

### 14.10 Adjuvant Treatment of GIST

- 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. (…)

- 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 50/50 HPF, or tumors ruptured into the peritoneal cavity. (…)

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

5 WARNINGS AND PRECAUTIONS

5.1 Fluid Retention and Edema

(…) In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Gleevec and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Gleevec and in 3.9% of patients receiving nilotinib 300 mg bid. (…) 5.3 Congestive Heart Failure and Left Ventricular Dysfunction

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

5.5 Hemorrhage

(…) 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 85 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, 776 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 increase 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 was described primarily as periorbital or lower limb edemas. These edemas were reported as Grade 3/4 events in 6.3% of the patients and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec.

6.7 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The safety profile in the HES/CEL patient population does not appear to be different from the safety profile of Gleevec observed in other hematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia, and anemia.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Gleevec have been demonstrated in pediatric patients with newly diagnosed Ph+ chronic phase CML and Ph+ ALL (see Clinical Studies (14.2, 14.4)). There are no data in children under 1 year of age.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Pediatric Use

(…) Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, Ph+ ALL, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in pediatric patients receiving 200 mg/m² once-daily (not exceeding 600 mg once-daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once-daily.

14 CLINICAL STUDIES

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<td>021588, 09/27/2016</td>
<td>Imatinib (3)</td>
<td>Oncology</td>
<td>PDGFRB</td>
<td>1 INDICATIONS AND USAGE</td>
<td>1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)</td>
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<td>Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)]. The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.</td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
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<td>2.6 Adult Patients with MDS/MPD</td>
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<td>Determine PDGFRB gene rearrangements status prior to initiating treatment. Information on FDA-approved tests for the detection of PDGFRB rearrangements is available at <a href="http://www.fda.gov/companiondiagnostics">http://www.fda.gov/companiondiagnostics</a>.</td>
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<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.5 Myelodysplastic/Myeloproliferative Diseases</td>
</tr>
</tbody>
</table>
|                                         |      |                 |            |                  | 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. (...)

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text†</th>
</tr>
</thead>
</table>
| 021868, 09/27/2016                     | Imatinib (4) | Oncology | FIP1L1-PDGFRα | Indications and Usage, Dosage and Administration, Clinical Studies | 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. (…)

14.6 Dermatofibrosarcoma Proteruberns

Dermatofibrosarcoma Proteruberns (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. (…)

(…)

(…)

For the 10 study patients with the PDGF B gene rearrangement there were 4 complete and 6 partial responses. The median duration of response in the phase 2 study was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.

<table>
<thead>
<tr>
<th>017090, 07/28/2014</th>
<th>Imipramine</th>
<th>Psychiatry</th>
<th>CYP2D6</th>
<th>Precautions</th>
<th>PRECAUTIONS</th>
</tr>
</thead>
</table>

14.6 Aggressive Systemic Masticytosis

(…)

Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality were predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the 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. (See Table 23) (…)

14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (See Table 24) (…)

<table>
<thead>
<tr>
<th>022383, 09/26/2014</th>
<th>Indacaterol</th>
<th>Pulmonary</th>
<th>UGT1A1</th>
<th>Clinical Pharmacology</th>
<th>12 CLINICAL PHARMACOLOGY</th>
</tr>
</thead>
</table>

12.4 Pharmacogenomics

The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA7/Ta7) genotype (low UGT1A1 expression; also referred to as *2B*) and the (TA6, (TA6 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the (TA7), (TA7) genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.

<table>
<thead>
<tr>
<th>761040, 08/17/2017</th>
<th>Inotuzumab Ozogamicin</th>
<th>Oncology</th>
<th>BCR-ABL1 (Philadelphia chromosome)</th>
<th>Clinical Studies</th>
<th>14 CLINICAL STUDIES</th>
</tr>
</thead>
</table>

Patients With Relapsed or Refractory ALL – INO-VATE ALL

Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. All patients were required to have ≥ 5% bone marrow blasts and to have received 1 or 2 previous induction chemotherapy regimens for ALL. Patients with Philadelphia chromosome-positive B-cell precursor ALL were required to have disease that failed treatment with at least 1 tyrosine kinase inhibitor and standard chemotherapy. (…)

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<th>Biomarker</th>
<th>Labeling Sections</th>
<th>Labeling Text</th>
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<tbody>
<tr>
<td>020571, 12/18/2014</td>
<td>Irinotecan</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Dosage and Administration, Warnings and Precautions, Clinical Pharmacology</td>
<td>When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPOTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele [see Dosage and Administration (2.1 and 2.2) and Warnings and Precautions (5.3)]. However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment (See Tables 1-4).</td>
</tr>
<tr>
<td>019790, 02/27/2013</td>
<td>Isoflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Contraindications</td>
<td>CONTRAINDICATIONS Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.</td>
</tr>
<tr>
<td>05706, 02/27/2013</td>
<td>Isoniazid, Pyrazinamide, and Rifampin</td>
<td>Infectious Diseases</td>
<td>Nonspecific (NAT)</td>
<td>Clinical Pharmacology</td>
<td>CLINICAL PHARMACOLOGY (...) Isoniazid is metabolized in the liver mainly by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50% of African Americans and Caucasians are “slow inactivators” and the rest are “rapid inactivators”; the majority of Eskimos and Asians are “rapid inactivators”. The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.</td>
</tr>
<tr>
<td>019700, 10/24/2014</td>
<td>Isosorbide Dinitrate</td>
<td>Cardiology</td>
<td>CYB5R</td>
<td>Overdosage</td>
<td>OVERDOSAGE Methemoglobinemia Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide dinitrate are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide dinitrate. In one study in which 39 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8-6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in typical toxic levels of nitroglycerin (1.2 mg/kg/hr).</td>
</tr>
</tbody>
</table>

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</table>
| 020215, 10/02/2014                     | Isosorbide Mononitrate | Cardiology | CYB5R | Overdosage | Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrates liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8-11.1 mg of isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to totally without cytochrome b5 reductase activity. In none of the affected patients had been thought to be unusually susceptible. None of the affected patients had been thought to be unusually susceptible.

343x389 Methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

<table>
<thead>
<tr>
<th>203188, 07/31/2017</th>
<th>Ivacaftor</th>
<th>Pulmonary</th>
<th>CFTR</th>
<th>Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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 bi-directional sequencing when recommended by the mutation test instructions for use.</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 clinical practice. The overall safety profile of KALYDECO is based on results from three placebo-controlled clinical trials conducted in 353 patients 6 years of age and older with one 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 (12.1) and Clinical Studies (14)]:

• An 8-week, crossover design trial (Trial 4) involving 39 patients between the ages of 6 and 57 years with a G1244E, G1349D, G178R, G551S, G907R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. 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, methemoglobinemia 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.

The proportion of patients who prematurely discontinued study drug due to adverse reactions was 2% for KALYDECO-treated patients and 5% for placebo-treated patients. Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in KALYDECO-treated patients included abdominal pain, increased hepatic enzymes, and hypoglycemia. 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%), sinusitis (6%), dizziness (6%), and bacteria in sputum (5%). The incidence of adverse reactions below is based upon two double-blind, placebo-controlled, 48-week clinical trials (Trials 1 and 2) in a total of 213 patients with CF ages 6 to 53 who have a G551D mutation in the CFTR gene and who were treated with KALYDECO 150 mg orally or placebo twice daily. Table 2 shows adverse reactions occurring in ≥2% 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 studies included the following CF patients:

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1. CLINICAL PHARMACOLOGY

1.1 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 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 2769+5G→A, 3272-26A→G, 3843+10k→C→T, 7113A→G and E831X and these are listed in Table 3 below [see also Clinical Studies (14.4)]. The G970R mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor [see Clinical Studies (14.2)].

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

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

12 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 -48 mmol/L (95% CI -57, -39). 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 5 years who had been administered either 50 mg or 75 mg of ivacaftor twice daily for 8 weeks (Trial 5), 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. (…)


The efficacy and safety of KALYDECO in patients with CF who have a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene were evaluated in a two-part, randomized, double-blind, placebo-controlled, crossover design clinical trial in 36 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 G1244E, S549N, S549R, 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 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 FBEV >40% predicted. (see Table 8) (…)

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<tr>
<td>210491, 02/12/2018</td>
<td>Ivacaftor and Tezacaftor</td>
<td>Pulmonary, CFTR</td>
<td>Specific Populations, Clinical Studies</td>
<td>ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. <strong>Limitations of Use</strong> The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation.</td>
<td></td>
</tr>
</tbody>
</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. 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 aged 6 through 11 years who are homozygous for the F508del mutation in the CFTR gene were obtained from a 24-week, open-label, multicenter Phase 3 safety trial (Trial 3). (…)

(…). Table 2 shows adverse reactions occurring in ≥5% of 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) (…)

(…). The safety profile from the 24-week, open-label, multicenter Phase 3 safety trial in 58 patients aged 6 through 11 years with CF who are homozygous for the F508del-CFTR mutation (Trial 3) was similar to that observed in Trials 1 and 2.

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 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. (…)

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| 204439, 04/28/2016 | Lacosamide | Neurology | CYP2C19 | 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=8) and extensive metabolizers (EM) (N=8) of cytochrome P450 (CYP) 2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations and the amount excreted into urine of the O-desmethyl metabolite were about 70% reduced in PMs compared to EMs. (see Table 9). The mean ppFEV1 at baseline was 60.0% [range: 27.8% to 96.2%]. (see Table 8 and Figure 2) (…) |
| 020406, 10/24/2016 | Lansoprazole | Gastroenterology | CYP2C19 | 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. (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 CFT 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. (…) |

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| 022059, 04/06/2017                     | Lapatinib (1) | 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:
• capcitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

**Limitation of Use:** Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capcitabine.
• letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that 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 capcitabine 2,000 mg/m2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended (see Clinical Pharmacology (12.3)). Capcitabine should be taken with food or within 30 minutes after food. If a day’s dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer
The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended (see Clinical Pharmacology (12.3)).

**2.2 Dose Modification Guidelines**

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

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

**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 lapatinib (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 lapatinib in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (Erbb2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab.

(…), Ninety-seven percent (97%) had stage IV breast cancer. 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were Erbb2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab. (…)

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| 022059, 04/06/2017                     | Lapatinib (2) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies | (...)
|                                        |      |                  |            |                  | 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 in women with HER2-positive metastatic 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 PgR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). Of all patients randomized to treatment, 219 (17%) patients had tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH) 2+ or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2- negative and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective was to evaluate and compare progression-free survival (PFS) in the HER2 positive population. Progression-free survival was defined as the interval of time between date of randomization and the earlier date of first documented sign of disease progression or death due to any cause. The baseline demographic and disease characteristics were balanced between the two treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty-four percent (84%) of the patients were white. Approximately 50% of the HER2-positive population had prior adjuvant/neoadjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab. In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 7 and Figure 3. (See Table 7 and Figure 3) |

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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). (...)

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

14 CLINICAL STUDIES

14.2 Clinical Trials in Subjects with Genotype 1 HCV

Treatment-Naïve Adults without Cirrhosis — ION-3 (Study 0108)

(…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated subjects, the median age was 55 years (range: 20 to 75); 58% of the subjects were male; 78% were White; 19% were Black; 6% were Hispanic or Latinx; mean body mass index was 28 kg/m² (range: 18 to 66 kg/m²); 81% had baseline HCVRNA levels greater than or equal to 800,000 IU per mL; 80% had genotype 1a HC virus infection; 73% had non-C/C IL28B alleles (CT or TT). (...)

Clinical Pharmacology

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic study of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among 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.

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<td>207888, 12/22/2015</td>
<td>Lesinurad</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS 7.1 CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 Inducers Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone), and in CYP2C9 poor metabolizers [see Clinical Pharmacology (12.3)]. (…)</td>
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<tr>
<td>207278, 01/15/2014</td>
<td>Letrozole</td>
<td>Oncology</td>
<td>ESR, PGR (Hormone Receptor)</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>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 antihormone therapy [see Clinical Studies (14.4, 14.5)].</td>
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6.1 Clinical Trials Experience Myelodysplastic Syndromes
A total of 148 patients received at least 1 dose of 10 mg REVLMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLMID. The most frequently reported adverse events were related to bone and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. Thrombocytopenia (61.5%, 91/148) and neutropenia (58.8%, 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%, 72/148), pruritus (41.9%, 62/148), rash (35.8%, 53/148) and fatigue (31.1%, 46/148). Table 9 summarizes the adverse events that were reported in ≥ 5% of the REVLMID-treated patients in the del 5q MDS clinical study. Table 9 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient’s underlying disease. (See Table 9)

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 REVLMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional 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. (…)
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<td>Lidocone and Prilocaine (1)</td>
<td>Anesthesiology</td>
<td>Nonspecific (Congenital Methemoglobinemia)</td>
<td>Warnings and Precautions</td>
<td>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 A randomized, double-blind, multinational trial compared Femara 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIB 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 III trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least antiestrogen therapy. (See Table 15) (...)</td>
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<td>021451, 08/08/2012</td>
<td>Lidocone and Prilocaine (2)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
<td>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 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 methHb-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, methHb levels are &lt;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 methHb in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5g Oraqix. (...)</td>
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<td>209229, 06/18/2018</td>
<td>Lofexidine</td>
<td>Anesthesiology</td>
<td>CYP2D6</td>
<td>Use in Specific Populations</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics (...) Patients with glucose-6-phosphate dehydrogenase deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to drug induced methemoglobinemia. [See Warnings and Precautions (5.1)] (...)</td>
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</table>
| 016832, 06/05/1998                   | Mafenide | Infectious Diseases | G6PD | Warnings, Adverse Reactions | WARNINGS Fatal hereditary anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate. ADVERSE REACTIONS (...) Fatal hereditary anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate. (...)

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<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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</tbody>
</table>

2.1 Maintenance Therapy

The recommended starting dose of PURIXAN in multi-agent combination chemotherapy maintenance regimens is 1.5 to 2.5 mg/kg (50 to 75 mg/m²) as a single daily dose. After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cytopenia. Evaluate thiopurine Smethyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression. Homozygous deficiency in either TPMT or NUDT15

2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression (see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)). Homozygous deficiency in either TPMT or NUDT15

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 (2.1, 2.2) and Clinical Pharmacology (12.5)).

Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by coadministration with drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression (see Drug Interactions (7.1, 7.3 and 7.4)).

12 CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

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

20039, 02/20/2018                      | Mercaptopurine (2) | Oncology | NUDT15 | Dosage and Administration, Warnings and Precautions, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION |

2.1 Maintenance Therapy

The recommended starting dose of PURIXAN in multi-agent combination chemotherapy maintenance regimens is 1.5 to 2.5 mg/kg (50 to 75 mg/m²) as a single daily dose. After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cytopenia. Evaluate thiopurine Smethyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression.
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| 204630, 04/08/2016                    | Methylene Blue | Hematology | G6PD        | Contraindications, Warnings and Precautions | Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]. Homozygous deficiency in either TPMT or NUDT15 is associated with a biologic effect. 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. 

**5 WARNINGS AND PRECAUTIONS**

**5.1 Myelosuppression**

The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia. Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)].

Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by coadministration with drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)].

**12 CLINICAL PHARMACOLOGY**

**12.5 Pharmacogenomics**

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the 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 allele of TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 65% 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 interfere with TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. 

**4 CONTRAINDICATIONS**

PROVAYBLUE™ is contraindicated in the following conditions:

- Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)].
- Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia [see Warnings and Precautions (5.3, 5.4)].

**5 WARNINGS AND PRECAUTIONS**

**5.3 Lack of Effectiveness**

Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to aryl amines such as aniline or sulf drugs such as diphenidol. Monitor response to therapy with PROVAYBLUE™ through resolution of methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a response, consider alternative treatment options [see Dosage and Administration (2.2)].

Patients with glucose-6-phosphate dehydrogenase deficiency may not reduce PROVAYBLUE™ to its active form in vivo. PROVAYBLUE™ may not be effective in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**5.4 Hemolytic Anemia**

Hemolysis can occur during treatment of methemoglobinemia with PROVAYBLUE™. Laboratory testing may show Heinz bodies, elevated indirect bilirubin and low haptoglobin, but the Coombs test is negative. The onset of anemia may be delayed 1 or more days after treatment with PROVAYBLUE™. The anemia may be due to red blood cell transfusions. [see Adverse Reactions (6.1)]. Use the lowest effective number of doses of PROVAYBLUE™ to treat methemoglobinemia. Discontinue PROVAYBLUE™ and consider alternative treatments of methemoglobinemia if severe hemolysis occurs.

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with PROVAYBLUE™ may result in severe hemolysis and severe anemia. PROVAYBLUE™ is contraindicated for use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency [see Contraindications (4)].

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<td>09/22/2011</td>
<td>Metoclopramide</td>
<td>Gastroenterology</td>
<td>CYB5R</td>
<td>Precautions,</td>
<td>PRECAUTIONS</td>
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<td>Overdosage</td>
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<td>Other Special Populations: Patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see Overdosage).</td>
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<td>OVERDOSEAGE</td>
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<td>PRECAUTIONS</td>
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<td>019962,</td>
<td>09/06/2014</td>
<td>Metoprolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions,</td>
<td>7 DRUG INTERACTIONS</td>
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<td>Clinical Pharmacology</td>
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<td>207997,</td>
<td>04/28/2017</td>
<td>Midostaurin</td>
<td>Oncology</td>
<td>FLT3</td>
<td>Indications and</td>
<td>1 INDICATIONS AND USAGE</td>
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<td>Usage, Dosage and</td>
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<tr>
<td>04/28/2017</td>
<td>Midostaurin (2)</td>
<td>Oncology</td>
<td>NPM1</td>
<td>Clinical Studies</td>
<td>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 LeukoStrati® 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. (…) 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 in the midostaurin arm and 60% of patients tested on the placebo arm. (…)</td>
</tr>
<tr>
<td>04/28/2017</td>
<td>Midostaurin (3)</td>
<td>Oncology</td>
<td>KIT</td>
<td>Clinical Studies</td>
<td>12 CLINICAL STUDIES</td>
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<td></td>
<td>14.2 Systemic Mastocytosis</td>
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<td>Study 2 (…) Of the 116 patients treated, a study steering committee identified 89 patients who had measurable C-findings and were evaluable for response. The median age in this group was 64 years (range: 25 to 82), 64% of patients were male, and nearly all patients (97%) were Caucasian. Among these patients, 36% had prior therapy for SM, and 52% had the KIT D816V mutation detected at baseline. Their median duration of treatment was 11 months (range: &lt; 1 to 68 months), with treatment ongoing in 17%. Efficacy was established on the basis of confirmed complete remission (CR) plus incomplete remission (ICR) by 6 cycles of RYDAPT by modified Valient criteria. Confirmed major or partial responses occurred in 46 of 73 patients with a documented KIT D816V mutation, 10 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. (…)</td>
</tr>
<tr>
<td>07/28/2017</td>
<td>Mirabegron</td>
<td>Urology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<tr>
<td>07/28/2017</td>
<td>Modafinil</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>01/15/2015</td>
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<td>12.3 Pharmacokinetics</td>
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<td></td>
<td>Metabolism Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although in vitro studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, in vivo results indicate that these isozymes play a limited role in the overall elimination. In healthy subjects who are genotypically poor metabolizers of CYP2D6, mean Cmax and AUCtau were approximately 66% and 17% higher than in extensive metabolizers of CYP2D6, respectively. In vitro and ex vivo studies have shown the involvement of butylincholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP2D6 and CYP2D6.</td>
</tr>
<tr>
<td>10/27/2015</td>
<td>Mycophenolic Acid</td>
<td>Transplantation</td>
<td>HPRT1</td>
<td>Warnings and Precautions</td>
<td>5.10 Rare Hereditary Deficiencies</td>
</tr>
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<td>Myofib is an inosine monophosphate dehydrogenase inhibitor (IMPDH inhibitor). Myofib should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphonosyl-transferase (HPGPT) such as Lesch-Nyhan and Kelley-DeMeulemaker 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, leuko, nephrotis, oligoarthropathy and renal disease including renal failure.</td>
</tr>
<tr>
<td>11/28/2012</td>
<td>Nalidixic Acid</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Precautions, Adverse Reactions</td>
<td>PRECAUTIONS (…) Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS) (…)</td>
</tr>
<tr>
<td>12/14/2011</td>
<td>Nebivolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
<td>2 DOSAGE AND ADMINISTRATION 2.2 Subpopulations</td>
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</thead>
</table>
| 070637, 07/17/2014 | Nefazodone | Psychiatry | CYP2D6 | Precautions | 12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
Nefazodone is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity. Plasma levels of d-nebivolol increase in proportion to dose in EMs and PMs for doses up to 20mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug’s activity as d-nebivolol’s beta receptor affinity is > 1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher Cmax and 10-fold higher AUC of d-nebivolol than do EMs. d-Nefazodone accumulates about 1.5-fold with repeated once-daily dosing in EMs.

020851, 07/17/2017 | Neratinib (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | 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 (14.1)).

020851, 07/17/2017 | Neratinib (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 14 CLINICAL STUDIES
14.1 Extended Adjuvant Treatment in Breast Cancer
The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. (…)

022068, 09/27/2016 | Nilotinib (1) | Oncology | BCR-ABL1 (Philadelphia chromosome) | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific | 1 INDICATIONS AND USAGE
1.1 Newly Diagnosed Ph+ CML-CP
Tasigna (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) in chronic phase. The effectiveness of Tasigna is based on major molecular response and cytogenetic response rates (see Clinical Studies (14.1)).

1.2 Resistant or Intolerant Ph+ CML-CP and CML-AP
Tasigna is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+CML) in adult patients resistant or intolerant to prior therapy that included imatinib. The effectiveness of Tasigna is based on hematologic and cytogenetic response rates (see Clinical Studies (14.2)).

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2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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<td>Newly Diagnosed Ph+ CML-CP</td>
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<tr>
<td>The recommended dose of Tasigna is 300 mg orally twice daily [see Clinical Pharmacology (12.3)].</td>
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<tr>
<td>Resistant or Intolerant Ph+ CML-CP and CML-AP</td>
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<tr>
<td>The recommended dose of Tasigna (nilotinib) is 400 mg orally twice daily [see Clinical Pharmacology (12.3)].</td>
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2.2 Dose Adjustments or Modifications

Other Non-hematologic Toxicities:

If other clinically significant moderate or severe non-hematologic toxicity develops, withhold dosing, and resume at 400 mg once daily when the toxicity has resolved. If clinically appropriate, escalation of the dose back to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily should be considered. For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Test serum lipase levels monthly or as clinically indicated. For Grade 3 to 4 bilirubin or hepatic transaminases elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Test bilirubin and hepatic transaminases levels monthly or as clinically indicated [see Warnings and Precautions (5.17)]. (See Table 2 and 4)

Concomitant Strong CYP3A4 Inhibitors

Avoid the concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nefinavir, ritonavir, saquinavir, telithromycin, voriconazole). Avoid grapefruit products since they may also increase serum concentrations of nilotinib. Should treatment with any of these agents be required, therapy with Tasigna should be interrupted. If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, consider a dose reduction 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. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period should be allowed before the Tasigna dose is adjusted upward to the indicated dose. For patients who cannot avoid use of strong CYP3A4 inhibitors, monitor closely for prolongation of the QT interval [see Boxed Warning, Warnings and Precautions (5.5, 5.6, Use in Specific Populations (8.7)]. (See Table 2 and 4)

5 WARNINGS AND PRECAUTIONS

5.12 Hemorrhage

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

5.17 Fluid Retention

In the randomized trial in patients with newly diagnosed Ph+ CML in chronic phase, severe (Grade 3 or 4) fluid retention occurred in 3.9% and 2.9% of patients receiving Tasigna 300 mg bid and 400 mg bid, respectively, and in 2.5% of patients receiving imatinib. (…) (See Table 5, 6, and 7)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In 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). (…)

In 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. (See Table 5, 6, and 7) (…)

6.2 Additional Data from Clinical Trials

(…)

6 USE IN SPECIFIC POPULATIONS

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. (…)

14 CLINICAL STUDIES

14.1 Newly Diagnosed Ph+ CML-CP

An open-label, multicenter, randomized trial was conducted to determine the efficacy of Tasigna versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. (See Table 9) (…)

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

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<td>Nilotinib (2)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>A single-arm, open-label, multicenter study was 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. (See Table 10) (…).</td>
</tr>
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<td>208447, 03/27/2017</td>
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<td>BRCA</td>
<td>Clinical Studies</td>
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<td>009175, 11/04/2013</td>
<td>Nitrofurantoin</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Warnings, Adverse Reactions</td>
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<td>125564, 12/20/2017</td>
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<td>BRAF</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
<td>6 ADVERSE REACTIONS</td>
</tr>
</tbody>
</table>

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### 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)].

### 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.**

### 12.5 Pharmacogenomics

**Tasigna** can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment. In this study, the (TA)/(TA) genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)/(TA) and (TA)/(TA) genotypes. However, the largest increases in bilirubin were observed in the (TA)/(TA) patients (see Warnings and Precautions (5.6)).**

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### 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**
  - **(…)** Was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. (…)

**CHECKMATE-067**
- **Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF-V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c).** (…)

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### Last Updated: 06/2018
### Table of Pharmacogenomic Biomarkers in Drug Labeling

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<tbody>
<tr>
<td>125554, 12/20/2017</td>
<td>Nivolumab (2)</td>
<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Clinical Pharmacology, Clinical Studies</td>
<td>(\ldots) Disease characteristics were: AJCC Stage IV disease (93%); 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%). (\ldots) 14.2 Adjuvant Treatment of Melanoma (\ldots) Disease characteristics were AJCC Stage IIIB (34%), Stage IIB (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%). (\ldots)</td>
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Table of Pharmacogenomic Biomarkers in Drug Labeling
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<tr>
<th>Number, Label Version Date</th>
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<tr>
<td>125554, 12/20/2017</td>
<td>Nivolumab (3)</td>
<td>Oncology</td>
<td>Microsatellite Instability, Mismatch Repair</td>
<td>Indications and Usage, Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td></td>
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<tr>
<td>018013, 07/28/2014</td>
<td>Nortriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td></td>
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</tbody>
</table>

had ≥1%, but <5% tumor cells with positive staining, 7% (16/246) had ≥5% but <10% tumor cells with positive staining, and 67% (165/246) had greater than or equal to 10% tumor cells with positive staining. Figure 9 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 10 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1. (see Figures 9 and 10) (…)

14.4 Renal Cell Carcinoma
CHECKMATE-025
(…) Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. (…) (O) OS benefit was observed regardless of PD-L1 expression level. (…)

14.5 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 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as ≥1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 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.

14.7 Urothelial Carcinoma
CHECKMATE-275
(…) Patients were included regardless of their PD-L1 status. Tumor specimens were evaluated prespectively 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 27)

1.8 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
OPDIVO 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 (14.8)]. 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.

8.4 Pediatric Use
The safety and effectiveness of OPDIVO have been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater for this indication is the same as that in adults [see Dosage and Administration (2.8), Clinical Pharmacology (12.5), and Clinical Studies (14.4)]. The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients less than 18 years old for the other approved indications.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in safety and efficacy between a nivolumab dose of 240 mg or 3 mg/kg every 2 weeks in patients with melanoma, NSCLC, RCC, urothelial carcinoma, MSI-H CRC, and HCC.

14 CLINICAL STUDIES
14.8 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
CHECKMATE-142 (NCT02060188) was a multicenter, open-label, single arm study conducted in patients with locally determined dMMR or MSI-H metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. (…)

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.
Table of Pharmacogenomic Biomarkers in Drug Labeling
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<th>Labeling Sections</th>
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<tr>
<td>125486, 02/26/2016</td>
<td>Obinutuzumab</td>
<td>Oncology</td>
<td>MSA1 (CD20 antigen)</td>
<td>Clinical Studies</td>
<td>ant ideators (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>
</tbody>
</table>
| 206162, 01/26/2017                     | Olaparib  | Oncology         | BRCA       | Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies | 14 CLINICAL STUDIES | 1.1 Treatment of gBRCA-mutated advanced ovarian cancer
Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The indication is approved under accelerated approval based on objective response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.|
| 761038, 10/19/2016                     | Otaratumab | Oncology         | PDGFRα     | Clinical Studies | 14 CLINICAL STUDIES | 1.4 Chronic Lymphocytic Leukemia
GAZYA 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 (CCr) < 70 mL/min. (…)|
| 203565, 06/01/2014                     | Omacetaxine | Oncology         | BCR-ABL1 (Philadelphia chromosome) | Clinical Studies | 14 CLINICAL STUDIES | 1.4 Chronic Lymphocytic Leukemia
Omacetaxine is indicated for the treatment of patients who have 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+]k) (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)|

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<td>207931, 02/14/2017</td>
<td>Ombitasvir, Paritaprevir, and Ritonavir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES</td>
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<td></td>
<td>14.1 Clinical Trial Results in Adults with Chronic GT4 HCV Infection without Cirrhosis</td>
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<td>(…) 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 relapers; 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). (…)</td>
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<td>022056, 12/19/2016</td>
<td>Omeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Drug Interactions, Clinical Pharmacology</td>
<td>7 DRUG INTERACTIONS</td>
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<td>Tacrolimus</td>
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<td>Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3)</td>
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<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.5 Pharmacogenomics</td>
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<td>CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19<em>1 allele is fully functional while the CYP2C19</em>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 &gt; intermediate metabolizers &gt; 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))</td>
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<tr>
<td>020007, 09/18/2014</td>
<td>Ondansetron</td>
<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Metabolism</td>
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<td>(…) The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolisers of CYP2D6 and those who were extensive metabolisers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo. (…)</td>
</tr>
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<td>Oncology</td>
<td>EGFR</td>
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<td>202810, 12/04/2015</td>
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<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings and Precautions</td>
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<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5 4 Serious Dermatological Reactions</td>
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</table>
| 207103, 02/19/2016                      | Palbociclib (1) | Oncology | ESR (Hormone Receptor) | 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:

- letrozole as initial endocrine based therapy in postmenopausal women, or
- fulvestrant in women with disease progression following endocrine therapy.

The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**6 ADVERSE REACTIONS**

**6.1 Clinical Studies Experience**

**Study 1: IBRANCE plus Letrozole**

Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus letrozole alone was evaluated in Study 1. The data described below reflect exposure to IBRANCE in 83 of 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of treatment in Study 1. (…)

**Study 2: IBRANCE plus Fulvestrant**

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

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2. The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastastic breast cancer who received at least 1 dose of treatment in Study 2. (…)

**14 CLINICAL STUDIES**

**Study 1: IBRANCE plus Letrozole**

Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

Study 1 was a randomized, open-label, multicenter study of IBRANCE plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. A total of 165 patients were randomized in Study 1. (…)

**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 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. (…)

| 207103, 02/19/2016                      | Palbociclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Adverse Reactions, Clinical Studies | **1 INDICATIONS AND USAGE**

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<td>021372, 09/18/2014</td>
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<td>Gastroenterology</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2. The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in Study 2. (…) 14 CLINICAL STUDIES Study 1: IBRANCE plus Letrozole Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy Study 1 was a randomized, open-label, multicenter study of IBRANCE plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. A total of 165 patients were randomized in Study 1. (…) 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 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. (…) 11 Pharmacokinetics Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.</td>
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<tr>
<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>6.1 Clinical Trials Experience (…) Safety data are presented from two clinical trials in which patients received Vectibix: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 20050203 are limited to 658 patients with wild-type KRAS mCRC. The safety profile of Vectibix in patients with wild-type RAS mCRC is similar with that seen in patients with wild-type KRAS mCRC.</td>
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<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>1.1 Metastatic Colorectal Cancer Vectibix is indicated for the treatment of patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) [see Dosage and Administration (2.1)], (…) 1.2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection Prior to initiation of treatment with Vectibix, assess RAS mutational status in colorectal tumors and confirm the absence of a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of both KRAS and NRAS. Information on FDA-approved tests for the detection of RAS mutations in patients with metastatic colorectal cancer is available at: <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</td>
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5 WARNINGS AND PRECAUTIONS
5.2 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with RAS-Mutant mCRC
Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereafter is referred to as “RAS” [see Indications and Usage (1.1), Dosing and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14)].

Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of RAS mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing RAS mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents [see Indications and Usage (1.1), and Clinical Pharmacology (12.1)].

Additionally, in Study 20050203, 272 patients with RAS-mutant mCRC tumors received Vectibix in combination with FOLFAX and 276 patients received FOLFAX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with RAS-mutant mCRC who received Vectibix and FOLFAX versus FOLFAX alone [see Indications and Usage (1.1)].

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

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

6.1 Clinical Trials Experience

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

(….) Vectibix in Combination with FOLFAX Chemotherapy

The most commonly reported adverse reactions (≥ 20%) in patients with wild-type KRAS mCRC receiving Vectibix (6 mg/kg every 2 weeks) and FOLFAX therapy (N = 320) in Study 20050203 were diarrhea, stomatitis, mucosal inflammation, ptosis, anemia, hypomagnesemia, hypocalcemia, rash, acneform dermatitis, pruritus, and dry skin (Table 2). Serious adverse reactions (≥ 2%) difference between treatment arms) in Vectibix-treated patients with wild-type KRAS mCRC were diarrhea and dehydration. The most commonly reported adverse reactions (1%) leading to discontinuation in patients with wild-type KRAS mCRC receiving Vectibix were rash, diaphoresis, fatigue, diarrhea, acneform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypocalcemia, 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 20050203, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type KRAS mCRC and in Study 20100007, an open-label, multicenter, multinational, randomized trial of 377 patients with wild-type KRAS mCRC. (….)

Study 20020408 (NCT00113763)

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

Study 20080763 (NCT01001377)

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

Study 20100007 (NCT01412957)

Study 20100007 was an open-label, randomized (1:1) clinical trial stratified by ECOG performance status (0 or 1 vs 2) and region (sites in Europe versus Asia versus rest of world) in patients with wild-type KRAS mCRC. Eligible patients were required to have received prior therapy with irinotecan, oxaliplatin, and a thymidylate synthase inhibitor, and have wild-type KRAS exon 2 mCRC as determined by a clinical trial assay. An assessment for RAS status (defined as KRAS exons 2, 3, and 4 and NRAS exons 2, 3, and 4) using Sanger sequencing was conducted in patients for whom tumor tissue was available.

Vectors (6 mg/kg intravenously every 14 days) plus BSC or BSC alone. Patients received Vectibix and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. The major efficacy outcome measure was OS in patients with wild-type KRAS mCRC. Secondary efficacy outcome measures included OS in the subgroup of patients with wild-type RAS mCRC, PFS and ORR in patients with wild-type KRAS, and PFS and ORR in the subgroup of patients with wild-type RAS mCRC.

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<td>212199, 01/04/2017</td>
<td>Paroxetine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
<td>BIOCHEMICAL FEATURES: Drug interactions</td>
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<td>Pazopanib (1)</td>
<td>Oncology</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
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<td>12.5 Pharmacogenomics</td>
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<td>Pazopanib can increase serum total bilirubin levels [see Warnings and Precautions (5.1)]. In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. A pooled pharmacogenetic analysis of 236 Caucasian patients evaluated the TA-repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during pazopanib treatment. In this analysis, the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic susceptibility to Gilbert’s syndrome) was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes.</td>
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<td>12.5 Pharmacogenomics</td>
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<td>In a pooled pharmacogenetic analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, ALT &gt; 3 X ULN (NCI CTC Grade 2) occurred in 32% (42/133) of HLA-B<em>57:01 allele carriers and in 19% (397/2101) of non-carriers and ALT &gt; 5 X ULN (NCI CTC Grade 3) occurred in 19% (25/133) of HLA-B</em>57:01 allele carriers and in 10% (213/2101) of non-carriers. In this dataset, 6% (133/2234) of the patients carried the HLA-B*57:01 allele. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype [see Warnings and Precautions (5.1)].</td>
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<tr>
<td>030349, 09/16/2015</td>
<td>Peginterferon Alfa-2b</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Pharmacology</td>
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<td>12.5 Pharmacogenomics</td>
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<td>A retrospective genome-wide association analysis1,2 of 1671 subjects (1604 subjects from Study 4 [see Clinical Studies (14.1)] and 67 subjects from another clinical trial) was performed to identify human genetic contributions to anti-HCV treatment response in previously untreated HCV genotype 1 subjects. A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (IL28B rs12979860) was associated with variable SVR rates. The rs12979860 genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1587), SVR rates by 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 rs1081342) 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>
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<tr>
<td>125293, 08/08/2016</td>
<td>Pegloticase</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information</td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.3 G6PD Deficiency Associated Hemolysis and Methemoglobinemia</td>
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<td>Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency; [see Contraindications (4)]. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency (4, 5.3).</td>
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<td>125514, 11/29/2017</td>
<td>Pembrolizumab (1)</td>
<td>Oncology</td>
<td>BRAF</td>
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<td>6.1 Clinical Trials Experience</td>
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<td>Oncology</td>
<td>CD274 (PD-L1)</td>
<td>Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies</td>
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(... A total of 634 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease, 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUC assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (48%) were previously treated with a BRAF inhibitor. (...)

| Ipilimumab-Refactory 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 one 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. (...)

| Pembrolizumab | (... Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease. (...)

| Melanoma | (... 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 one 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. (...)

| Ipilimumab-Naïve Melanoma | (... 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 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease. (...)

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<td>Microsatellite Instability, Mismatch Repair</td>
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<td>Recommend Dosage for MSI-H Cancer</td>
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### Keytruda (Pembrolizumab): Indications and Usage

**1 INDICATIONS AND USAGE**

1.6 Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaplatin, and irinotecan [see Clinical Studies (14.6)].

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

2 DOSAGE AND ADMINISTRATION

2.7 Recommended Dosage for MSI-H Cancer

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| 010775, 05/10/2002                    | Perphenazine | Psychiatry | CYP2D6 | Precautions, Clinical Pharmacology | Metabolism of a number of medications, including antipsychotics, antidepressants, β-blockers, and antiarrhythmics, occurs through the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called “poor metabolizers.” Among other populations the prevalence is not known. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at steady state, 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. (…)

125409, 03/22/2016 | Pertuzumab (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies | The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests. (See Tables 24 and 25) | 14.7 Gastric Cancer | (…)

125409 | Pertuzumab (1) | Oncology | ERBB2 (HER2) | Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies | The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests. (See Tables 24 and 25) | 14.7 Gastric Cancer | (…)

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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
Malignant Breast Cancer (MBC) (…)
6.2 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 was evaluated in a subgroup of 20 patients with HER2-positive metastatic breast cancer treated in Study 1. No 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 or 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. (…)

(…) Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab. (…)

14.2 Neoadjuvant Treatment of Breast Cancer
Study 2 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 (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PR) positivity. (…)

(…) 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. (…)

125499 03/22/2016 Pertuzumab (2) Oncology ESR, PGR (Hormone Receptor) Clinical Studies 14 CLINICAL STUDIES
14.1 Metastatic Breast Cancer (…) Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor

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<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 and CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. (…)</td>
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<td>010151, 06/16/2016</td>
<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 and CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. (…)</td>
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<tr>
<td>010151, 06/16/2016</td>
<td>Phenytoin (3)</td>
<td>Neurology</td>
<td>HLA-B</td>
<td>Warnings</td>
<td>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/Multiorgan 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. 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). Adults 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.</td>
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### Table of Pharmacogenomic Biomarkers in Drug Labeling

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| 018147, 05/09/2016                     | Ponatinib | Oncology | BCR-ABL1 (Philadelphia chromosome) | Clinical Pharmacology | 1 INDICATIONS AND USAGE

Iclusig (ponatinib) is a kinase inhibitor indicated for the:

- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
- Treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

Limitations of use

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)].

### WARNINGS AND PRECAUTIONS

#### 5.1 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>Prasugrel (1)</td>
<td>Cardiology</td>
<td>CYP2C19</td>
<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
<td>Two patients (&lt;1%) treated with liciusg 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 liciusg. 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, 3 BP-CML; 0 Ph+ ALL), and the median duration of treatment with liciusg 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 liciusg were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (40%) as compared with patients &lt; 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a similar hematologic response rate (45%) as compared with patients &lt; 65 years of age (44%). (…) 8.9 Metabolic Status In healthy subjects, patients with stable athersclerosis, 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</td>
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| 022307, 07/12/2016 | Prasugrel (2) | Cardiology | CYP2C9 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.  
14 CLINICAL STUDIES (…) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…) |
| 022307, 07/12/2016 | Prasugrel (3) | Cardiology | CYP3A5 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.  
14 CLINICAL STUDIES (…) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…) |
| 022307, 07/12/2016 | Prasugrel (4) | Cardiology | CYP2B6 | Use in Specific Populations, Clinical Pharmacology, Clinical Studies | There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.  
14 CLINICAL STUDIES (…) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…) |
| 008316, 06/22/2017 | Primaquine (1) | Infectious Diseases | G6PD | Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage | CONTRAINDICATIONS Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings).  
WARNINGS Hemolytic anemia and G6PD deficiency |

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<td>008316, 06/22/2017</td>
<td>Primaquine (2)</td>
<td>Infectious Diseases</td>
<td>CYB5R</td>
<td>Precautions, Adverse Reactions</td>
<td>Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Primaquine should not be prescribed for patients with severe G6PD deficiency (see Contraindications). In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. Discontinue the use of primaquine phosphate promptly if signs suggestive of hemolytic anemia occur (darkening of the urine, marked fall of hemoglobin or erythrocytic count). Hemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia, and Oceania. People from these regions have a greater tendency to develop hemolytic anemia (due to a congenital deficiency of erythrocytic G6PD) while receiving primaquine and related drugs. Usage in Pregnancy: Safe usage of this preparation in pregnancy has not been established. Primaquine is contraindicated in pregnant women. Even if a pregnant woman is G6PD normal, the fetus may not be (see Contraindications).</td>
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<td>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>The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor [see Warnings and Precautions (5.4) and Drug Interactions (7.1)].</td>
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Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.

7 DRUG INTERACTIONS

7.1 CYP2D6 and CYP3A4 Inhibitors

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

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Metabolism

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encaïnine, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.

As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics is linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The larger inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity [see Dosage and Administration (2)].

Inter-Subject Variability

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

PRECAUTIONS

7.1 CYP2D6 and CYP3A4 Inhibitors

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). (...) 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 produgs 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.

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<td>021438, Propranolol</td>
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<tr>
<td>07/17/2014</td>
<td>073644, Protriptyline</td>
</tr>
<tr>
<td>02/22/2010</td>
<td>089338, Quinidine</td>
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</tbody>
</table>

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Table of Pharmacogenomic Biomarkers in Drug Labeling
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<tr>
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<tbody>
<tr>
<td>021799, 07/02/2014</td>
<td>Quinine Sulfate</td>
<td>Infectious Diseases</td>
<td>G6PD</td>
<td>Contraindications</td>
<td>4 CONTRAINDICATIONS QUALAQUN 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</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 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>020973, 04/04/2016</td>
<td>Rabeprazole</td>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 12.3 Pharmacogenomics Metabolism CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug. Drug Interaction Studies Combined Administration with Antimicrobials Sixteen healthy subjects genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg ACIPHEX delayed-release tablets, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. (…) Clopidogrel Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects including CYP2C19 extensive and intermediate metabolizers receiving once daily administration of clopidogrel 75 mg concomitantly with placebo or with 20 mg ACIPHEX delayed-release tablets (n=36), for 7 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 12% (mean AUC ratio was 88 %, with 90% CI of 81.7 to 95.5) when ACIPHEX delayed-release tablets were coadministered compared to administration of clopidogrel with placebo [see Drug Interactions (7)]. 12.5 Pharmacogenomics In a clinical study in evaluating ACIPHEX delayed-release tablets in Japanese adult patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. The clinical relevance of this is not known. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.</td>
</tr>
<tr>
<td>022145, 03/05/2018</td>
<td>Raltegravir</td>
<td>Infectious Diseases</td>
<td>UGT1A1</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY 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/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09). In the neonatal study IMPAACT P1110, there was no association between apparent clearance (CL/F) of raltegravir and UGT1A1 genotype polymorphisms.</td>
</tr>
<tr>
<td>103846, 06/13/2016</td>
<td>Rasburicase (1)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS Hemolysis Do not administer Elitek to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Elitek if hemolysis occurs. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek therapy (4, 5.2).</td>
</tr>
<tr>
<td>103846, 06/13/2016</td>
<td>Rasburicase (2)</td>
<td>Oncology</td>
<td>CYB5R</td>
<td>Contraindications, Warnings and Precautions</td>
<td>BOXED WARNING WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS Methemoglobinemia Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek if methemoglobinemia occurs (4, 5.3).</td>
</tr>
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</table>
| 209092, 03/13/2017                    | Ribociclib (1) | Oncology | ESR, PGR (Hormone Receptor) | Indications and Usage, Clinical Studies | 4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.3 Methemoglobinemia

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

1 INDICATIONS AND USAGE

KISQALI® 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.

14 CLINICAL STUDIES

Study 1 (MONALEESA-2) was a randomized, double-blind, placebo-controlled, multicenter clinical study of KISQALI® plus letrozole versus placebo plus letrozole conducted in postmenopausal women with HR-negative, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. (…)

| 209092, 03/13/2017 | Ribociclib (2) | Oncology | ERBB2 (HER2) | Indications and Usage, Clinical Studies | 1 INDICATIONS AND USAGE

KISQALI® 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)-positive advanced or metastatic breast cancer.

14 CLINICAL STUDIES

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| 020722, 03/01/2016 | Risperidone | Psychiatry | CYP2D6 | Drug Interactions, Clinical Pharmacology | 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 (n=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. (…)

12 CLINICAL PHARMACOLOGY

Metabolism

(…) CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antihypertensives, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and its inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone vary less between these two groups (…) The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL CONSTA® administration is 3 to 6 days, and is associated with a monoe xponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 Lh and 5.0 Lh in extensive CYP 2D6 metabolizers, and 3.3 Lh and 3.2 Lh in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL CONSTA®. The elimination phase is complete approximately 7 to 8 weeks after the last injection. (…)

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-progressive (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.

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<tbody>
<tr>
<td>Rosuvastatin</td>
<td>Endocrinology</td>
<td>SLC01B1</td>
<td>Clinical Pharmacology</td>
<td>12.5 Pharmacogenomics</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Disposition of HMG-CoA reductase inhibitors, including rosvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T &gt; C). The frequency of this genotype (i.e., SLCO1B1 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosvastatin has not been clearly established.</td>
</tr>
<tr>
<td>Rucaparib (1)</td>
<td>Oncology</td>
<td>BRCA</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies</td>
<td>1.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rubraca is indicated for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca [see Dosage and Administration (2.1)].</td>
</tr>
</tbody>
</table>

**2 DOSAGE AND ADMINISTRATION**

2.2 Recommended Dosage 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 Rubraca maintenance eight weeks following completion of Rubraca in combination with chemotherapy. Administer Rubraca 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 Rubraca administered as a single agent [See Clinical Studies (14.1)]. Most patients received Rubraca 375 mg/m² weekly for 4 doses. (…)

6 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 Rubraca 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 Rubraca 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 Rubraca 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 Rubraca 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 Rubraca in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,882 patients. (…)

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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 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 by the FoundationFocus™ CDx BRCA LOH test for 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 99% (177/178) of BRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the BRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the 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 to 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 108 patients in two multicenter, single-arm, open-label clinical trials. Study 10 (NCT01482715) and ARIEL2 (NCT01891344), 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 58 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 18/108 patients (17%) who had deleterious BRCA mutations detected in tumor tissue and not in whole blood specimens. Tumor BRCA mutation status was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the companion diagnostic FoundationFocus™ CDxBRCA test, which is FDA approved for selection of patients for Rubraca treatment. (see Table 7)

Response assessment by independent radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 45]) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation.

15 Adverse Reactions

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.

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<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
<td>12 CLINICAL PHARMACOLOGY</td>
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<td>12.3 Pharmacokinetics</td>
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<td>Specific Populations</td>
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<td></td>
<td>CYP Enzyme Polymorphism</td>
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<td>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>
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<td>CYP1A2</td>
<td>Clinical Pharmacology</td>
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<td>12.3 Pharmacokinetics</td>
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<td>600478, 03/11/2014</td>
<td>Sevoflurane</td>
<td>Anesthesiology</td>
<td>Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)</td>
<td>Warnings</td>
<td>WARNINGS</td>
</tr>
<tr>
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<td>Malignant Hyperthermia in susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Sevoflurane can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, 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-acute-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.</td>
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| 205123, 02/14/2017                     | Simeprevir | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology, Clinical Studies | 12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics

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

14 CLINICAL STUDIES
14.2 OLYSIO in Combination with Sofosbuvir

#### Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection

(….) These 59 subjects had a median age of 57 years (range: 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, and 24% Black or African American. 40% had a BMI greater than or equal to 30 kg/m², the median baseline HCV RNA level was 6.7 log10 IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0-F1, F2 and F3, respectively, and 29% had HCV genotype 1a of which 41% carried Q80K at baseline, and 25% had HCV genotype 1b; 14% had IL28B CC genotype, 64% IL28B CT genotype, and 22% IL28B TT genotype; 75% were prior null responders to Peg-IFN-alfa and RBV; and 25% were treatment-naïve.

**OPTIMIST-1** was an open-label, randomized Phase 3 trial in HCV 1-infected subjects without cirrhosis who were treatment-naïve or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred fifty-five subjects without cirrhosis receiving 12 weeks of OLYSIO with sofosbuvir. The 155 subjects without cirrhosis receiving 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]) and with IL28B CC and non-CC genotypes (34/35 [100%] and 107/112 [96%], respectively).

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

#### Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection

(….) In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the OLYSIO and placebo treatment groups. In the pooled analysis of trials (QUEST 1 and QUEST 2), the 785 enrolled subjects had a median age of 47 years (range: 19 to 70 years; with 2% above 65 years); 52% were male; 78% were White, 20% Black or African American, and 16% Hispanic; 37% had a BMI ≤ 30 kg/m²; the median baseline HCV RNA level was 6.83 log10 IU/mL; 75% had HCV genotype 1a of which 40% had Q80K polymorphism at baseline, and 25% had HCV genotype 1b; 28% had IL28B CC genotype, 55% IL28B CT genotype, and 17% IL28B TT genotype.

#### Treatment-Naïve East Asian Subjects with HCV Genotype 1 Infection

(….) These 304 subjects had a median age of 45 years (range: 18 to 68 years; with 2% above 65 years); 49% were male; all were East Asians (81% were enrolled in Japan, 19% were enrolled in South Korea); 3% had a BMI greater than or equal to 30 kg/m², 84% had baseline HCV RNA levels greater than 80000 IU/mL; 74% had METAVIR fibrosis score F0, F1 or F2, 16% METAVIR fibrosis score F3, and 10% METAVIR fibrosis score F4 (cirrhosis); 48% had HCV genotype 1a, and 51% HCV genotype 1b; 29% had IL28B CC genotype, 50% IL28B CT genotype, and 15% IL28B TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a and RBV; in QUEST 2, 69% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b.

Table 17 shows the response rates in treatment-naïve adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR12 rates were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. (See Table 17) (….) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%], respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]) and with IL28B CC and non-CC genotypes (34/35 [100%] and 107/112 [96%], respectively).

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<td>203822, 02/14/2012 Sodium Nitrite</td>
<td>Toxicology</td>
<td>G6PD</td>
<td>Warnings and Precautions</td>
<td>above 65 years; 66% were male; 93% were White, 3% Black or African American, and 2% Asian; 27% had a BMI greater than or equal to 30 kg/m²; 85% had baseline HCV RNA levels greater than 800 000 IU/mL; 54% had METAVIR fibrosis score F0, F1, or F2, 16% METAVIR fibrosis score F3, and 18% METAVIR fibrosis score F4 (cirrhosis); 43% had HCV genotype 1a, and 57% HCV genotype 1b; 17% had IL28B CC genotype, 67% IL28B CT genotype, and 16% IL28B TT genotype (information available for 93 subjects); 27% of the overall population and 23% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. Forty percent (40%) of subjects were prior relapsers, 35% prior partial responders, and 25% prior null responders following prior therapy with Peg-IFN-alfa and RBV. Demographics and baseline characteristics were balanced between the 12 weeks 150 mg OLYSIO and placebo treatment groups. (See Table 21) SVR24 rates were higher in the OLYSIO-treated subjects compared to subjects receiving placebo in combination with Peg-IFN-alfa and RBV, regardless of HCV geno/subtype, METAVIR fibrosis score, and IL28B genotype. Subjects with HCV/HIV-1 Co-Infection (…) The 106 enrolled subjects in the C212 trial had a median age of 48 years (range: 27 to 67 years; with 2% above 65 years); 85% were male; 82% were White, 14% Black or African American, 1% Asian, and 3% Hispanic; 12% had a BMI greater than or equal to 30 kg/m²; 86% had baseline HCV RNA levels greater than 800 000 IU/mL; 68% had METAVIR fibrosis score F0, F1 or F2, 16% METAVIR fibrosis score F3, and 13% METAVIR fibrosis score F4; 82% had HCV genotype 1a, and 17% HCV genotype 1b; 28% of the overall population and 34% of the subjects with genotype 1a had Q80K polymorphism at baseline; 27% had IL28B CC genotype, 56% IL28B CT genotype, and 17% IL28B TT genotype; 50% (n=53) were HCV treatment-naïve subjects, 14% (n=15) prior relapsers, 9% (n=10) prior partial responders, and 26% (n=28) prior null responders. (…) Adult Subjects with HCV Genotype 4 Infection (…) The 107 enrolled subjects in the RESTORE trial with HCV genotype 4 had a median age of 49 years (range: 27 to 69 years; with 5% above 65 years); 76% were male; 72% were White, 28% Black or African American, and 7% Hispanic; 14% had a BMI greater than or equal to 30 kg/m²; 60% had baseline HCV RNA levels greater than 800 000 IU/mL; 57% had METAVIR fibrosis score F0, F1 or F2, 14% METAVIR fibrosis score F3, and 29% METAVIR fibrosis score F4; 42% had HCV genotype 4a, and 24% had HCV genotype 4b; 6% had IL28B CC genotype, 56% IL28B CT genotype, and 35% IL28B TT genotype; 50% (n=53) were treatment-naïve HCV subjects, 21% (n=22) prior relapsers, 9% (n=10) prior partial responders, and 37% (n=40) prior null responders. (…)</td>
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<td>204971, 02/14/2012 Sofosbuvir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Clinical Trials in Subjects with Genotype 1 or 4 HCV Treatment-Naïve Adults — NEUTRINO (Study 110) (…) SVR12 rates were 99% (89/90) in subjects with genotype 1 or 4 HCV and baseline IL28B C/C allele and 87% (200/230) in subjects with genotype 1 or 4 HCV and baseline IL28B non-C/C alleles. It is estimated that the SVR12 in patients who previously failed pegylated interferon and ribavirin therapy will approximate the observed SVR12 in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment (Table 9). The SVR12 rate in the NEUTRINO trial in genotype 1 subjects with 12/22 non-C/C alleles, HCV RNA greater than 800 000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52). (See Table 9) 14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1 (…) In subjects with HCV genotype 1 infection, the SVR12 rate was 82% (74/90) in subjects with genotype 1a infection and 54% (13/24) in subjects with genotype 1b infection, with relapse accounting for the majority of treatment failures. SVR12 rates in subjects with HCV genotype 1 infection were 80% (24/30) in subjects with baseline IL28B C/C allele and 75% (62/83) in subjects with baseline IL28B non-C/C alleles. (…)</td>
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<tr>
<td>208341, 02/14/2017 Sofosbuvir and Velpatasvir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td>14 CLINICAL STUDIES 14.2 Clinical Trials in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis Genotype 4, 5, and 6 HCV Infected Adults (ASTRAL-4) (…) Demographics and baseline characteristics were balanced between the EPCLUSA and placebo group. Of the 740 treated subjects, the median age was 56 years (range: 18 to 82); 60% of the subjects were male; 79% were White; 9% were Black; 21% had a baseline body mass index at least 30 kg/m²; the proportions of subjects with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5%, and 7%, respectively; 66% 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 5 HCV Infected Adults (ASTRAL-5) (…) 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); 59% of the subjects were male; 88% were White; 7% were Black; 33% had a baseline body mass index at least 30 kg/m²; 62% had non-CC IL28B alleles (CT or TT); 90% had baseline HCV RNA levels at least 800 000 IU/mL; 14% had compensated cirrhosis; and 15% were treatment-experienced. (…) 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; 96% 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, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5%, and 7%, respectively; 66% 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. (…)</td>
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<td>Sofosbuvir, Velpatasvir, and Voxilaprevir</td>
<td>Infectious Diseases</td>
<td>IFNL3 (IL28B)</td>
<td>Clinical Studies</td>
<td><strong>Proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 78%, 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 B cirrhosis at screening, 6% and 4% of subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment. (…)</strong></td>
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<td>019988, 07/16/2007</td>
<td>Succimer</td>
<td>Hematology</td>
<td>G6PD</td>
<td>Clinical Pharmacology</td>
<td><strong>Clinical Studies</strong></td>
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<td>Succinylcholine</td>
<td>Anesthesiology</td>
<td>BCHE</td>
<td>Warnings, Precautions</td>
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<td>Infectious Diseases</td>
<td>G6PD</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>Non-specific (NAT)</td>
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<td>Precautions</td>
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| 017970, 03/09/2006                     | Tamoxifen (1) | Oncology      | ESR, PGR (Hormone Receptor) | Indications and Usage, Precautions, Adverse Reactions, Clinical Studies | INDICATIONS AND USAGE
Metastatic Breast Cancer

NOLVADEX is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, NOLVADEX is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

Adjuvant Treatment of Breast Cancer

(…) The estrogen and progesterone receptor values may help to predict whether adjuvant NOLVADEX therapy is likely to be beneficial. (…)

PRECAUTIONS

Reduction in Breast Cancer Incidence in High Risk Women

(…) Women should understand that NOLVADEX reduces the incidence of breast cancer, but may not eliminate risk. NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. In women with breast cancer who are at high risk of developing a second breast cancer, treatment with about 5 years of NOLVADEX reduced the annual incidence rate of a second breast cancer by approximately 50%. (…)

ADVERSE REACTIONS

Adjuvant Breast Cancer

(…) Anastrozole Adjuvant Trial - Study of Anastrozole compared to NOLVADEX for Adjuvant Treatment of Early Breast Cancer (see CLINICAL PHARMACOLOGY - Clinical Studies). At a median follow-up of 33 months, the combination of anastrozole and NOLVADEX did not demonstrate any efficacy benefit when compared to NOLVADEX therapy given alone in all patients as well as in the hormone receptor positive subgroup. This 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 NOLVADEX 20 mg, respectively. (…)

CLINICAL STUDIES

Adjuvant Breast Cancer

(…) 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 unknown breast cancer, 58% were entered into trials comparing NOLVADEX to no adjuvant therapy and 42% were entered into trials comparing NOLVADEX in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node positive disease and 46% had node negative disease.

Node Positive - Individual Studies
In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50-59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while there was a nonsignificant trend toward adverse effect in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60-70 years, there was a trend toward a beneficial effect of NOLVADEX without any clear relationship to estrogen or progesterone receptor status.

Node Negative - Individual Studies
NSABP B-14, a prospective, double-blind, randomized study, compared NOLVADEX to placebo in women with axillary node-negative, estrogen receptor positive (≥10 fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). (…) One additional randomized study (NATO) demonstrated improved disease-free survival for NOLVADEX compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of NOLVADEX appeared to be independent of estrogen receptor status.

Reduction in Breast Cancer Incidence in High Risk Women

(…) Table 4 describes the characteristics of the breast cancers in the NSABP P-1 trial and includes tumor size, nodal status, ER status. NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. (See Table 4) (…)

| 017970, 03/08/2006 | Tamoxifen (2) | Oncology | F5 (Factor V Leiden) | Warnings | Thromboembolic Effects of NOLVADEX
There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during NOLVADEX therapy. When NOLVADEX is coadministered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of NOLVADEX should be carefully considered in women with a history of thromboembolic events. In a small substudy (N=81) of the NSABP P-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 NOLVADEX therapy. |

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| 017970, 03/08/2006                     | Tamoxifen (3) | Oncology         | F2 (Prothrombin) | Warnings | WARNINGS
|                                        |                  |                  |                  |                  | Thromboembolic Effects of NOLVADEX
|                                        |                  |                  |                  |                  | There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during NOLVADEX therapy. When NOLVADEX is coadministered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of NOLVADEX should be carefully considered in women with a history of thromboembolic events. In a small substudy (N=81) of the NSABP P-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 NOLVADEX therapy. |
| 201917, 10/28/2013                     | Telaprevir      | Infectious Diseases | IFNL3 (IL28B) | Clinical Pharmacology, Clinical Studies | 12.5 Pharmacogenomics
|                                        |                  |                  |                  |                  | A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR). rs12979860 was genotyped in 454 of 1088 subjects in Trial 108 (treatment-naive) and 527 of 662 subjects in Trial C216 (previously treated) [see Clinical Studies (14.2 and 14.3) for trial descriptions]. SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naive subjects receiving PR48 (Table 9). Among both treatment-naive and previous treatment failures, subjects with all IL28B genotypes appeared to have higher SVR rates with regimens containing INCIVEK. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences in demographic or clinical characteristics of the subpopulation relative to the overall trial population. In Trial C211, all subjects were prospectively tested for IL28B variants; there were no clinically relevant differences in SVR12 responses between q8h and twice-daily dosing within the genetic subgroups. (See Table 9) |
| 021894, 06/03/2015                     | Tetrabenazine   | Neurology         | CYP2D6       | Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 2 DOSAGE AND ADMINISTRATION
|                                        |                  |                  |                  |                  | 2.2 Individualization of Dose
|                                        |                  |                  |                  |                  | Dosing Recommendations Above 50 mg per day Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
|                                        |                  |                  |                  |                  | 2.2.1 Extensive and Intermediate CYP2D6 Metabolizers
|                                        |                  |                  |                  |                  | Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse reactions such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepresants) [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
|                                        |                  |                  |                  |                  | 2.2.2 Poor or Extensive CYP2D6 Metabolizers
|                                        |                  |                  |                  |                  | Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosing and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].
|                                        |                  |                  |                  |                  | 5 WARNINGS AND PRECAUTIONS
|                                        |                  |                  |                  |                  | 5.2 Laboratory Tests
|                                        |                  |                  |                  |                  | Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are poor metabolizers (PMs), extensive (EMs) or intermediate metabolizers (IMs) of XENAZINE. Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient’s CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg [see Dosing and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
|                                        |                  |                  |                  |                  | 8 USE IN SPECIFIC POPULATIONS
|                                        |                  |                  |                  |                  | 8.7 Poor or Extensive CYP2D6 Metabolizers
|                                        |                  |                  |                  |                  | Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosing and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].
|                                        |                  |                  |                  |                  | Poor Metabolizers
|                                        |                  |                  |                  |                  | Poor CYP2D6 metabolizers (PMs) 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

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<td>12.5 Pharmacogenetics</td>
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<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>
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**Laboratory Tests**

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

**CLINICAL PHARMACOLOGY**

### Metabolism and Genetic Polymorphism

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1528 children with ALL, the approximate tolerated mercaptopurine dosage range that patients with TPMT 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, 50-50%; 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 or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the "2" and "3" alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient’s actual TPMT activity.

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<td><strong>CYP2D6</strong></td>
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| **Boxed Warning, Warnings, Precautions, Use in Specific Populations, Clinical Pharmacology** | **ULTRAM.** extreme sleepiness, confusion, or shallow breathing) (see OVERDOSAGE). Therefore, individuals who are ultra-rapid metabolizers should not use regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol (see WARNINGS). **WARNINGS** Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-Threatening Respiratory Depression in Children Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol 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 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see OVERDOSAGE). Therefore, individuals who are ultra-rapid metabolizers should not use ULTRAM. **PRECAUTIONS**

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<td>Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children</td>
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**Advising 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 a ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol.

Because of the risk of life-threatening respiratory depression and death:
- ULTRAM is contraindicated for all children younger than 12 years of age (see CONTRAINDICATIONS).
- 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 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 45% lower.

Some populations are poor/ultra-rapid metabolizers of CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower.

### 2 INDICATIONS AND USAGE

**MEKINIST** is indicated, as a single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Clinical Studies (14.1)].

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

MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Clinical Studies (14.2)].

### 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)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

**NSCLC**

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.2)]. Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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

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

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**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 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol.

Because of the risk of life-threatening respiratory depression and death:
- ULTRAM is contraindicated for all children younger than 12 years of age (see CONTRAINDICATIONS).
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**CLINICAL PHARMACOLOGY**

**Metabolism**

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 45% lower.

Some populations are poor/ultra-rapid metabolizers of CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower.

### 2 INDICATIONS AND USAGE

**MEKINIST** is indicated, as a single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Clinical Studies (14.1)].

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

MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Clinical Studies (14.2)].

### 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)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

**NSCLC**

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.2)]. Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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

MEKINIST Administered as a Single Agent

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

MEKINIST Administered with Dabrafenib

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

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

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

### 12 CLINICAL PHARMACOLOGY

#### 12.2 Pharmacodynamics

Administration of 1 mg and 2 mg MEKINIST to patients with BRAF V600E mutation-positive melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis).

#### 12.3 Pharmacokinetics

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

### 14 CLINICAL STUDIES

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

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

Mektinist with Dabrafenib

The safety and efficacy of MEKINIST administered with dabrafenib were evaluated in an international, randomized, double-blind, active-controlled trial (the COMBi-d study; NCT01586468). The COMBi-d study compared dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive MEKINIST 2 mg once daily plus dabrafenib 150 mg twice daily or dabrafenib 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (greater than the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR). In the COMBi-d study, 423 patients were randomized to MEKINIST plus dabrafenib (n = 211) or dabrafenib plus placebo (n = 212). The median age was 56 years (range: 22 to 99 years), 53% were male, >99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIc, 66% had M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing with the FDA-approved companion diagnostic test; 85% had BRAF V600E mutation-positive melanoma and 15% had BRAF V600K mutation-positive melanoma.

#### 14.2 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

In Study BRF113928 (NCT01336634), the safety and efficacy of dabrafenib alone or administered with MEKINIST were evaluated in a multicenter, three-cohort, open-label, 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 Oncorine™ Dx Target Test, the ORR results were similar to those presented in Table 11.

### 15 Lack of Clinical Activity in Metastatic Melanoma Following BRAF/Inhibitor Therapy

The clinical activity of MEKINIST as a single agent was evaluated in a single-arm, multicenter, international trial in 40 patients with BRAF V600E or V600k mutation-positive, unresectable or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received MEKINIST at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity.

The median age was 58 years, 63% were male, all were White, 88% had baseline ECOG PS of 0 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No patient achieved a confirmed partial or complete response as determined by the clinical investigators.

### 17 PATIENT COUNSELING INFORMATION

**Confirmation of BRAF V600E or V600K mutation**

Evidence of BRAF V600E or V600K mutation within the tumor specimen is necessary to identify patients for whom treatment with MEKINIST is indicated [see Dosage and Administration (2.1)].

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<td>(… The trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVO or RPED, QTcB interval ≥480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency. (…))</td>
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<td>ERBB2 (HER2)</td>
<td>Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies</td>
<td>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</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• as a part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel</td>
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<td></td>
<td></td>
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<td>• with docetaxel and carboplatin</td>
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<td>• as a single agent following multi-modality anthracycline based therapy.</td>
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<td>1.2 Metastatic Breast Cancer Herceptin is indicated:</td>
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<td></td>
<td></td>
<td></td>
<td>• In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer</td>
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<td></td>
<td></td>
<td>• As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.</td>
</tr>
<tr>
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<td>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.</td>
</tr>
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<td></td>
<td>5.1 New Primary Malignancies Non-Cutaneous Malignancies 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% (193) of patients receiving Mekinist with dabrafenib. Monitor patients receiving Mekinist and dabrafenib closely for signs or symptoms of non-cutaneous malignancies. No dose modification is required for Mekinist in patients who develop non-cutaneous malignancies [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

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</table>
| 103792, 03/17/2016 | Trastuzumab (2) | Oncology | ESR, PGR (Hormone Receptor) | Clinical Studies | 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 by a central laboratory. (…) (…) Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). (…) Study 4 In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. (…) (…) Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 10. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH+ unknown and the FISH +IHC unknown subgroups. (See Table 10) (…) 14.2 Metastatic Breast Cancer The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab. Previously Untreated Metastatic Breast Cancer (Study 5) Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). (…) (…) Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (See Table 12). (…) Previously Treated Metastatic Breast Cancer (Study 6) Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. (…) 14.3 Metastatic Gastric Cancer The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%). (…) (…) An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14. (See Table 14) 14 CLINICAL STUDIES 14.1 Adjuvant Breast Cancer Study 4 (…) The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and/or PR-negative) (n = 1603), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2446), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.88). (…) 020438, 07/01/2008 Tretinoin Oncology PML-RARA Indications and Usage, Warnings, Clinical Pharmacology INDICATIONS AND USAGE VESANOVID (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARA gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. VESANOVID is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with VESANOVID. WARNINGS Patients Without the t(15;17) Translocation * Therapeutic areas do not necessarily reflect the CDER review division. † Representative biomarkers are listed based on standard nomenclature as per the Human Genome Organization (HUGO) symbol and/or simplified descriptors using other common conventions. Listed biomarkers do not necessarily reflect the terminology used in labeling. 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| 016792, 07/17/2014                     | Trenipramine | Psychiatry | CYP2D6 | Precautions | Drugs Metabolized by P450 2D6. The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among 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 the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. (…)
| 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 mg) (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 | Dose and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology | 5 WARNINGS AND PRECAUTIONS
5.2 QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant [see Clinical Pharmacology (12.2)]. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. (…)

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<td>POLG</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
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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>4 CONTRAINdications</td>
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<tr>
<td>204249, 11/06/2017</td>
<td>Vemurafenib (1)</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage</td>
<td>1 INDICATIONS AND USAGE</td>
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</tbody>
</table>

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**5.1 Hepatotoxicity**

Patients with Known or Suspected Mitochondrial Disease

Depakene is contraindicated in patients known to have mitochondrial disorders caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents. POLG-related disorders should be suspected in patients with a family history of UCD or a family history of unexplained infant deaths (particularly males); those with a family history of UCD or a family history of unexplained infant deaths; those with a family history of UCD or a family history of unexplained infant deaths; and those with a family history of UCD or a family history of unexplained infant deaths. POLG mutation testing should be performed in accordance with current clinical practice for the diagnosis 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)].

**5.6 Urea Cycle Disorders (UCD)**

Vamproic acid is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders [see Contraindications (4) and Warnings and Precautions (5.6)].

**5.9 Hyperammonemia**

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should also be considered in patients who present with hypothermia [see Warnings and Precautions (5.1)]. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders [see Contraindications (4) and Warnings and Precautions (5.6, 5.10)].

Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

**4 CONTRAINdications**

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

---

**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 mutations in the gene for mitochondrial DNA polymerase γ (POLG) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents. POLG-related disorders should be suspected in patients with a family history of UCD or a family history of unexplained infant deaths (particularly males); those with a family history of UCD or a family history of unexplained infant deaths; those with a family history of UCD or a family history of unexplained infant deaths; and those with a family history of UCD or a family history of unexplained infant deaths. POLG mutation testing should be performed in accordance with current clinical practice for the diagnosis of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders.

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Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.
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<td>Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
<td>Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td></td>
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<td>1.2 Erdheim-Chester Disease</td>
<td>ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.</td>
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<td></td>
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<td>2 DOSAGE AND ADMINISTRATION</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1 Patient Selection</td>
<td>Confirm the presence of BRAF V600E mutation in melanoma tumor specimens prior to initiation of treatment with ZELBORAF [see Warnings and Precautions (5.2)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at <a href="http://www.fda.gov/CompanionDiagnosics">http://www.fda.gov/CompanionDiagnosics</a>.</td>
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<td></td>
<td>5 WARNINGS AND PRECAUTIONS</td>
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<td>5.1 New Primary Malignancies</td>
<td>(…) Other Malignancies</td>
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<td>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.</td>
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<tr>
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<td>5.2 Tumor Promotion in BRAF Wild-Type Melanoma</td>
<td>In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation in tumor specimens prior to initiation of ZELBORAF [see Indications and Usage (1) and Dosage and Administration (2.1)].</td>
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</table>
|                                        |            |            | 5.5 QT Prolongation | Concentration-dependent QT prolongation occurred in an uncontrolled, open-label QT sub-study in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [see Clinical Pharmacology (12.2)]. (…)

### 6 ADVERSE REACTIONS

**6.1 Clinical Trials Experience**

(…) Unresectable or Metastatic Melanoma with BRAF V600E Mutation

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

This section describes adverse reactions identified from analyses of Trial 4 [see Clinical Studies (14)]. In Trial 4, 22 patients with BRAF V6000 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 V6000 mutation-positive ECD patients treated with ZELBORAF.

In Trial 4, the most commonly reported adverse reactions (> 50%) in patients with BRAF V6000 mutation-positive ECD treated with ZELBORAF were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma. The most common (≥ 10%) Grade ≥ 3 adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculo-papular, and arthralgia. (…)

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

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

Cardiac Electrophysiology

In a multi-center, open-label, single-arm study in 132 patients with BRAF V6000 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. (…) Other Malignancies

**12.3 Pharmacokinetics**

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

**14 CLINICAL STUDIES**

Treatment-Naive Patients with BRAF V6000 Mutation-Positive Unresectable or Metastatic Melanoma

Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naive, BRAF V6000 mutation-positive unresectable or metastatic melanoma, as detected by the cobas® 4800 BRAF V6000 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) (…)

In Trial 2, 132 patients with BRAF V6000 mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V6000 Mutation Test, who had received at least one prior systemic therapy, received ZELBORAF 960 mg by mouth twice daily. (…)
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<td>Oncology</td>
<td>Chromosome 17p</td>
<td>Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies</td>
<td>Patients with BRAF V600E Mutation-Positive Melanoma with Brain Metastases: The activity of ZELBORAF for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in an open-label, multicenter, single-arm, two cohort trial (Trial 3). (See Table 6)… Patients with Wild-Type BRAF Melanoma: ZELBORAF has not been studied in patients with wild-type BRAF melanoma (see Warnings and Precautions (5.2)). 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 V600E mutation-positive diseases. (…)</td>
</tr>
<tr>
<td>020151, 12/22/2012</td>
<td>Venlafaxine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Precautions</td>
<td>Drugs that inhibit Cytochrome P450 isoenzymes CYP2D6 Inhibitors: In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism and venlafaxine. However, although imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine and lower plasma concentrations of ODV, the total concentration of active compounds (venlafaxine plus ODV) was not affected. Additionally, in a clinical study involving CYP2D6-deficient and extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Ketocazole: A pharmacokinetic study with ketoconazole 100 mg b.i.d. with a single dose of venlafaxine 50 mg in extensive metabolizers (EM; n = 14) and 25 mg in poor metabolizers (PM; n = 6) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desvenlafaxine (ODV) in most subjects following administration of ketoconazole. Venlafaxine Cmax increased by 26% in EM subjects and 48% in PM subjects. Cmax values for ODV increased by 14% and 29% in EM and PM subjects, respectively. Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects (range in PMs 4% to 134%), and AUC values for ODV increased by 23% and 33% in EM and PM subjects (range in PMs -38% to 105%), respectively. Combined AUCs of venlafaxine and ODV increased on average by approximately 23% in EMS and 53% in PMs (range in PMs 4% to 134%). (…)</td>
</tr>
<tr>
<td>206873, 04/11/2016</td>
<td>Zelboraf</td>
<td>Oncology</td>
<td>RAS</td>
<td>Warnings and Precautions, Adverse Reactions</td>
<td>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.</td>
</tr>
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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA. Blue text represents the most recent additions and/or changes since last posted version.
Table of Pharmacogenomic Biomarkers in Drug Labeling
Last Updated: 06/2018

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<tr>
<th>NDA/ANDA/BLA Number, Label Version Date</th>
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<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Labeling Sections</th>
<th>Labeling Text‡</th>
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</table>
| 021266, 02/03/2015                     | Warfarin (1) | Hematology | CYP2C9 | Dosage and Administration, Drug Interactions, Clinical Pharmacology | 12 CLINICAL PHARMACOLOGY 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 dosing regimen than patients without these CYP variants. (See Table 1) |

12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics
Metabolism
The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic cytochrome P-450 (CYP450) microsomal enzymes to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols) with minimal anticoagulant activity. Identified metabolites of warfarin include dehydrowarfarin, two diastereoisomer alcohols, and 4′-hydroxywarfarin. The CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP2A6, and CYP3A4. 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 CLINICAL PHARMACOLOGY 12.5 Pharmacogenomics
CYP2C9 and VKORC1 Polymorphisms
The S-anomer 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, *7, *8, and 10-hydroxywarfarin. The CYP450 enzymes involved in the metabolism of warfarin include CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP2A6, and CYP3A4. 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)]. |

009218, 09/08/2016 | Voriconazole | Infectious Diseases | CYP2C19 | Clinical Pharmacology | Metabolism
VKORC1 and CYP2C9 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. Certain single nucleotide polymorphisms in the VKORC1 gene (e.g., –1639G>A) have been associated with variable warfarin dose requirements. Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle through inhibition of VKOR, a multiprotein enzyme complex. Identified metabolites of warfarin include dehydrowarfarin, two diastereoisomer alcohols, and 4′-hydroxywarfarin. The CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP2A6, and CYP3A4. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the in vivo anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance [see Clinical Pharmacology (12.5)]. |

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| 009218, 09/08/2016                   | Warfarin (2) | Hematology | VKORC1 | Dosage and Administration, Clinical Pharmacology | **2 DOSAGE AND ADMINISTRATION**

**2.3 Initial and Maintenance Dosing**

The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by:

- Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities
- Genetic factors (CYP2C9 and VKORC1 genotypes) [see Clinical Pharmacology (12.5)]

**Dosing Recommendations without Consideration of Genotype**

If the patient’s CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg once daily. Determine each patient’s dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily.

**Dosing Recommendations with Consideration of Genotype**

Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see Clinical Pharmacology (12.5)]. If the patient’s CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants. (See Table 1)

**12 CLINICAL PHARMACOLOGY**

**12.5 Pharmacogenomics**

CYP2C9 and VKORC1 Polymorphisms

The S-enantiomer of warfarin is mainly metabolized to 7-hydroxypolamin 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 multienzyme complex.

**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: (…) 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. (…)

**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 6 hours and 30 hours, respectively.

**5 WARNINGS AND PRECAUTIONS**

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