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

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)

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
020977, 03/20/2017	Abacavir	Infectious Diseases	HLA-B	Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions	**BOXED WARNING** WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY *Hypersensitivity Reactions* Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with ZIAGEN® (abacavir). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele [see Warnings and Precautions (5.1)]. ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients [see Contraindications (4), Warnings and Precautions (5.1)]. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible [see Contraindications (4), Warnings and Precautions (5.1)]. Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity [see Warnings and Precautions (5.1)]. (…) **2 DOSAGE AND ADMINISTRATION** **2.1 Screening for HLA-B*5701 Allele Prior to Starting ZIAGEN** Screen for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN [see Boxed Warning, Warnings and Precautions (5.1)]. **4 CONTRAINDICATIONS** ZIAGEN is contraindicated in patients: • who have the HLA-B*5701 allele [see Warnings and Precautions (5.1)]. **5 WARNINGS AND PRECAUTIONS** **5.1 Hypersensitivity Reactions** Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir). These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with ZIAGEN (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment [see Adverse Reactions (6.1)]. Patients who carry the HLA B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making. Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with ZIAGEN: • All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-B*5701 allele assessment. • ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. • Before starting ZIAGEN, review medical history for prior exposure to any abacavir containing product. NEVER restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status. • To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue ZIAGEN immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). • If a hypersensitivity reaction cannot be ruled out, do not restart ZIAGEN or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death, can occur within hours. • If a hypersensitivity reaction is ruled out, patients may restart ZIAGEN. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating 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.
208716, 08/17/2018	Abemaciclib (1)	Oncology	ESR (Hormone Receptor)	Indications and Usage, Adverse	**1 INDICATIONS AND USAGE** **VERZENIO™ (abemaciclib) is indicated:**

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

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				Reactions, Clinical Studies	• in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. • in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. • as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. **6 ADVERSE REACTIONS** **MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial EndocrineBased Therapy** *Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting* MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician's choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm. (…) ***MONARCH 2: VERZENIO in Combination with Fulvestrant*** *Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy* The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2. (…) ***VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)*** *Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting* Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months. (…) **14 CLINICAL STUDIES** **VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) (*MONARCH 3)*** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting* MONARCH 3 was a randomized (2:1), double-blinded, placebo-controlled, multicenter study in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer. (…) ***VERZENIO in Combination with Fulvestrant (MONARCH 2)*** *Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy* MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. (…) ***VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)*** *Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting* MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. (…)
208716, 08/17/2018	**Abemaciclib (2)**	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **VERZENIO™ (abemaciclib) is indicated:** • in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. • in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. • as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. **6 ADVERSE REACTIONS** **MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial EndocrineBased Therapy** *Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting* MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician's choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm.

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Last Updated: 06/2019

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					MONARCH 2: VERZENIO in Combination with Fulvestrant *Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy* The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2. (…) ***VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)*** *Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting* Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months. (…) **14 CLINICAL STUDIES** **VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) (MONARCH 3)** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting* MONARCH 3 was a randomized (2:1), double-blinded, placebo-controlled, multicenter study in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer. ***VERZENIO in Combination with Fulvestrant (MONARCH 2)*** *Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy* MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. (…) ***VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)*** *Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting* MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. (…)
125427, 05/03/2019	**Ado-Trastuzumab Emtansine**	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Metastatic Breast Cancer (MBC)** KADCYLA®, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy. **1.2 Early Breast Cancer (EBC)** KADCYLA, as a single agent, is indicated for the adjuvant treatment of patients with HER2- positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab -based treatment. Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA [see Dosage and Administration (2.1)] **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1), Clinical Studies (14)]. Assessment of HER2 protein overexpression and/or HER2 gene amplification should be performed using FDA-approved tests specific for breast cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CcompanionDiagnostics. Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the WARNINGS AND PRECAUTIONS reflect exposure to KADCYLA as a single agent at 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) in 1624 patients including 884 patients with HER2-positive metastatic breast cancer and 740 patients with HER2- positive early breast cancer (KATHERINE trial). Metastatic Breast Cancer In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2- positive metastatic breast cancer. The most common (≥ 25%) adverse reactions were fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation and epistaxis.

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Last Updated: 06/2019

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					The adverse reactions described in Table 3 were identified in patients with HER2-positive metastatic breast cancer treated in the EMILIA trial [see Clinical Studies (14.1)]. Patients were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.5 months and 5.3 months for patients treated with lapatinib and capecitabine, respectively. (…) Early Breast Cancer KADCYLA has been evaluated as a single-agent in 740 patients with HER2-positive early breast cancer. The adverse reactions described in Table 5 were identified in patients with HER2-positive early breast cancer treated in the KATHERINE trial [see Clinical Studies (14.2)]. Patients were randomized to receive KADCYLA or trastuzumab. The median duration of study treatment was 10 months for patients in the KADCYLA-treated group and 10 months for patients treated with trastuzumab. (…) **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Cardiac Electrophysiology The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., > 20 ms) were detected in the study. **12.3 Pharmacokinetics** *Effect of Hepatic Impairment* The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (ChildPugh B; n=8) hepatic impairment. (…) **14 CLINICAL STUDIES** **14.1 Metastatic Breast Cancer** The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial (EMILIA) (NCT00829166) of 991 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only prior adjuvant therapy were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. (…) **14.2 Early Breast Cancer** KATHERINE (NCT01772472) was a randomized, multicenter, open-label trial of 1486 patients with HER2-positive, early breast cancer. Patients were required to have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory using Ventana's PATHWAY anti-HER2-/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluation after preoperative therapy. KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. (…) The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 94% of these patients received pertuzumab. (…)
201292, 01/12/2018	**Afatinib**	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer** GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see Clinical Pharmacology (12.1) and Clinical Studies (14.1)]. Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations [see Clinical Studies (14.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC** 2.1 Patient Selection for Non-Resistant EGFR Mutation-Positive Metastatic NSCLC Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of nonresistant EGFR mutations in tumor specimens [see Indications and Usage (1.1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/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.(…) *EGFR Mutation-Positive, Metastatic NSCLC*

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Last Updated: 06/2019

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					(…) The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 3). (…) **14 CLINICAL STUDIES** **14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer** The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall 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 (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions was evaluated in a pooled analysis of such patients enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148], LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT01121393]). • LUX-Lung 2 was a single arm, multicenter study of afatinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue. • LUX-Lung 3 was a randomized, multicenter study comparing treatment with afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 every 21 days for up to 6 cycles. EGFR status was determined by the therascreen® EGFR 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 0, 63% had an ECOG PS 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIIb disease, and 88% had received no prior systemic therapy for advanced or metastatic disease. The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.
208434, 06/05/2018	**Alectinib**	Oncology	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** ALECENSA is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of metastatic NSCLC with ALECENSA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Previously Untreated ALK-Positive Metastatic NSCLC* The safety of ALECENSA was evaluated in 152 patients with ALK-positive NSCLC in the ALEX study. The median duration of exposure to ALECENSA was 17.9 months. (…) *ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib* The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with ALECENSA in two clinical trials, Studies NP28761 and NP28673. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects. In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration (Cmax,ss) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. (…) *Absorption*

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Last Updated: 06/2019

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					Alectinib reached maximal concentrations at 4 hours following administration of ALECENSA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC. (…) *Distribution* The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4. Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration. Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma. (…) *Elimination* The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC. **14 CLINICAL STUDIES** *Previously Untreated ALK-Positive Metastatic NSCLC* The efficacy of ALECENSA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ALEX: NCT02075840). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. (…) *ALK-Positive Metastatic NSCLC Previously Treated with Crizotinib* The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials: NP28761 (NCT01588028) and NP28673 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDAapproved test, and ECOG PS of 0-2 were enrolled in both studies. (…)
212526, 05/24/2019	**Alpelisib (1)**	Oncology	ERBB2 (HER2)	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CAmutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDAapproved tests for the detection of PIK3CA mutations in breast cancer is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)]. (…) **14 CLINICAL STUDIES** SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s). Overall, 60% of enrolled patients had tumors with one or more PIK3CA mutations in tissue, 50% had liver/lung metastases, and 6% had previously been treated with a CDK4/6 inhibitor. (...)
212526, 05/24/2019	**Alpelisib (2)**	Oncology	ESR (Hormone Receptor)	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CAmutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDAapproved tests for the detection of PIK3CA mutations in breast cancer is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

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					The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14)]. (…) **14 CLINICAL STUDIES** SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s). Overall, 60% of enrolled patients had tumors with one or more PIK3CA mutations in tissue, 50% had liver/lung metastases, and 6% had previously been treated with a CDK4/6 inhibitor. (…)
212526, 05/24/2019	**Alpelisib (3)**	Oncology	PIK3CA	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CAmutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with PIQRAY, based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens [see Clinical Studies (14)]. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDAapproved tests for the detection of PIK3CA mutations in breast cancer is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **14 CLINICAL STUDIES** SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s). Overall, 60% of enrolled patients had tumors with one or more PIK3CA mutations in tissue, 50% had liver/lung metastases, and 6% had previously been treated with a CDK4/6 inhibitor. There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. Of the 341 patients in the cohort with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the FDA-approved therascreen® PIK3CA RGQ PCR Kit. Out of the 336 patients with PIK3CA mutations confirmed in tumor tissue, 19 patients had no plasma specimen available for testing with the FDA-approved therascreen® PIK3CA RGQ PCR Kit. Of the remaining 317 patients with PIK3CA mutations confirmed in tumor tissue, 177 patients (56%) had PIK3CA mutations identified in plasma specimen, and 140 patients (44%) did not have PIK3CA mutations identified in plasma specimen. (…) (…) Patient demographics for those with PIK3CA-mutated tumors were generally representative of the broader study population. The median duration of exposure to PIQRAY plus fulvestrant was 8.2 months with 59% of patients exposed for > 6 months. (…) (…) The major efficacy outcome was investigator-assessed progression-free survival (PFS) in the cohort with a PIK3CA mutation per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall response rate (ORR) and overall survival (OS) in the cohort with a PIK3CA mutation. Efficacy results for the cohort with a PIK3CA mutation in tumor tissue are presented in Table 8 and Figure 1. PFS results for the cohort with a PIK3CA mutation by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. Consistent results were seen in patients with tissue or plasma PIK3CA mutations. At the time of final PFS analysis, 27% (92/341) of patients had died, and overall survival follow-up was immature. No PFS benefit was observed in patients whose tumors did not have a PIK3CA tissue mutation (HR = 0.85; 95% CI: 0.58, 1.25). (See Table 8 and Figure 1)
209321, 05/06/2019	**Amifampridine**	Neurology	NAT2	Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.5 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers** The recommended starting dosage of RUZURGI in pediatric patients weighing 45 kg or more who are known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily taken orally in divided doses. The recommended starting dosage in pediatric patients weighing less than 45 kg who are known NAT2 poor metabolizers is 7.5 mg daily taken orally in divided doses [see Dosage and Administration (2.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.5)]. **6 ADVERSE REACTIONS** **(…)** Subjects classified as poor metabolizers based on rate of metabolism were more likely to experience adverse reactions during RUZURGI treatment than intermediate or normal metabolizers [see Clinical Pharmacology (12.5)]. (…) **8 USE IN SPECIFIC POPULATIONS**

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

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					8.8 NAT2 Poor Metabolizers Exposure of RUZURGI is increased in patients who are N-acetyltransferase (NAT2) poor metabolizers [see Clinical Pharmacology (12.5)]. Therefore, initiate RUZURGI in patients who are known NAT2 poor metabolizers at the lowest recommended starting dosage and monitor for adverse reactions [see Dosage and Administration (2.5)]. Consider dosage modification of RUZURGI for patients who are known NAT2 poor metabolizers as needed based on clinical effect and tolerability. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Cardiac Electrophysiology The effect of RUZURGI on QTc interval prolongation was studied in a double-blind, randomized, placebo- and positive-controlled study in 52 healthy volunteers (including 23 subjects with poor metabolizer phenotype). Study participants were administered 120 mg RUZURGI in 4 equal doses of 30 mg at 4-hour intervals (Dose 1, 2, 3, and 4)[see Clinical Pharmacology (12.5)]. RUZURGI did not prolong the QTc interval to any clinically relevant extent. In vitro, RUZURGI did not inhibit the human ether-à-go-go-related gene ion channel. **12.5 Pharmacogenomics** Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of RUZURGI metabolism. In normal healthy volunteers, poor metabolizers, also referred to as "slow acetylators" (i.e., carriers of two reduced function alleles) had higher average plasma amifampridine concentrations than intermediate metabolizers, also referred to as "intermediate acetylators" (i.e., carriers of one reduced and one normal function alleles), and normal metabolizers, also referred to as "fast/rapid acetylators" (i.e., carriers of two normal function alleles). In the TQT study [see Clinical Pharmacology (12.2)], poor metabolizers (N=19) had 1.1 to 3.7 times higher AUC0-4h and 1.3 to 3.7 times higher Cmax than intermediate metabolizers (N=21), following the first dose. Poor metabolizers had 6.0 to 8.5 times higher AUC0-4h and 6.1 to 7.6 times higher Cmax than normal metabolizers (N=3), following the first dose. In the general population, the NAT2 poor metabolizer phenotype prevalence is 40–60% in the White and African American populations, and in 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent).
208078, 11/28/2018	**Amifampridine Phosphate**	Neurology	NAT2	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.4 Known N-acetyltransferase 2 (NAT2) Poor Metabolizers** The recommended starting dosage of FIRDAPSE in known N-acetyltransferase 2 (NAT2) poor metabolizers is 15 mg daily, taken orally in 3 divided doses [see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3, 12.5)]. **8 USE IN SPECIFIC POPULATIONS** **8.8 NAT2 Poor Metabolizers** Exposure of FIRDAPSE is increased in patients who are N-acetyltransferase 2 (NAT2) poor metabolizers [see Clinical Pharmacology (12.5)]. Therefore, initiate FIRDAPSE in patients who are known NAT2 poor metabolizers at the lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions [see Dosage and Administration (2.4)]. Consider dosage modification of FIRDAPSE for patients who are known NAT2 poor metabolizers as needed based on clinical effect and tolerability. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** The effect of FIRDAPSE on QTc interval prolongation was studied in a double blind, randomized, placebo and positive controlle d study in 52 healthy individuals who are slow acetylators. At an exposure 2-fold the expected maximum therapeutic exposure of amifampridine, FIRDAPSE did not prolong QTc to any clinically relevant extent. **12.5 Pharmacogenomics** Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of FIRDAPSE metabolism. Poor metabolizers, also referred to as "slow acetylators" (i.e., carriers of two reduced function alleles), have 3.5- to 4.5-fold higher Cmax, and 5.6- to 9- fold higher AUC than normal metabolizers, also referred to as "fast/rapid acetylators" (i.e., carriers of two normal function alleles). Therefore, FIRDAPSE should be initiated at the lowest recommended starting dosage (15 mg/day) in known NAT2 poor metabolizers, and such patients should be closely monitored for adverse reactions [see Dosage and Administration (2.4) and Use in Specific Populations (8.8)]. In the general population, the NAT2 poor metabolizer phenotype prevalence is 40–60% in the White and African American populations, and in 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent).
085971, 07/17/2014	**Amitriptyline**	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** **Drugs Metabolized by P450 2D6** The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. (…)
072691, 07/17/2014	**Amoxapine**	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** **Drug Interactions** **Drugs Metabolized by P450 2D6**

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Last Updated: 06/2019

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					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. 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. (…)
204325, 09/15/2017	Amphetamine	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** **Elimination** **Metabolism and Excretion** Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4 hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.
020541, 12/13/2018	Anastrozole	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Adjuvant Treatment** ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. **1.2 First-Line Treatment** ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer. **1.3 Second-Line Treatment** ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER negative disease and patients who did not respond to previous tamoxifen therapy 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 risedronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture. (…) **7 DRUG INTERACTIONS** **7.1 Tamoxifen** Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial [see Clinical Studies (14.1)]. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole. (…) **14 CLINICAL STUDIES** **14.1 Adjuvant Treatment of Breast Cancer in Postmenopausal Women** At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. (…) Patients in the two monotherapy arms of the ATAC trial were treated for a median of 60 months (5 years) and followed for a median of 68 months. Disease-free survival in the intent-to-treat population was statistically significantly improved [Hazard Ratio (HR) = 0.87, 95% CI: 0.78, 0.97, p=0.0127] in the ARIMIDEX arm compared to the tamoxifen arm. In the hormone receptor-positive subpopulation representing about 84% of the trial patients, disease-free survival was also statistically significantly improved (HR = 0.83, 95% CI: 0.73, 0.94, p=0.0049) in the ARIMIDEX arm compared to the tamoxifen arm. (See Figure 2) (…) The frequency of individual events in the intent-to-treat population and the hormone receptor-positive subpopulation are described in Table 8. (see Tables 7 and 8) A summary of the study efficacy results is provided in Table 9. (See Table 9, 10, and Figure 4) (…) **14.2 First-Line Therapy in Postmenopausal Women with Advanced Breast Cancer** Two double-blind, controlled clinical studies of similar design (0030, a North American study and 0027, a predominately European study) were conducted to assess the efficacy of ARIMIDEX compared with tamoxifen as first-line therapy for hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer in postmenopausal women. (See Table 11) (…) **14.3 Second-Line Therapy in Postmenopausal Women with Advanced Breast Cancer who had Disease Progression following Tamoxifen Therapy** Anastrozole was studied in two controlled clinical trials (0004, a North American study; 0005, a predominately European study) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. Some of the patients had also

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Last Updated: 06/2019

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					received previous cytotoxic treatment. Most patients were ER-positive; a smaller fraction were ER-unknown or ER negative; the ER-negative patients were eligible only if they had had a positive response to tamoxifen. (…)
021912, 05/29/2019	Arformoterol (1)	Pulmonary	UGT1A1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation 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.
021912, 05/29/2019	Arformoterol (2)	Pulmonary	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation 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.
021436, 02/23/2017	Aripiprazole	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments for Cytochrome P450 Considerations** Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response. (See Table 2) **8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2D6 Poor Metabolizers** Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see DOSAGE AND ADMINISTRATION (2.7) and CLINICAL PHARMACOLOGY (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** (…) For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours. *Drug Interaction Studies* Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors. (…) *Studies in Specific Populations* Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with Abilify (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults. (See Figure 4 and 5)
207533, 11/30/2018	Aripiprazole Lauroxil	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.4 Dose Adjustments for CYP450 Considerations** Refer to the prescribing information for oral aripiprazole for recommendations regarding dosage adjustments due to drug interactions, for the first 21 days when the patient is taking oral aripiprazole concomitantly with the first dose of ARISTADA. Once stabilized on ARISTADA, refer to the dosing recommendations below for patients taking CYP 2D6 inhibitors, CYP 3A4 inhibitors, or CYP 3A4 inducers: • No dosage changes recommended for ARISTADA, if CYP 450 modulators are added for less than 2 weeks. • Make dose changes to ARISTADA if CYP 450 modulators are added for greater than 2 weeks. (See Table 4) **8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2D6 Poor Metabolizers** Dosage adjustment is recommended in known CYP 2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and Elimination*

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Last Updated: 06/2019

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					(…) Elimination of aripiprazole is mainly through hepatic metabolism involving CYP 3A4 and CYP 2D6. Dosage adjustments are recommended in CYP 2D6 poor metabolizers due to high aripiprazole concentrations [see Dosage and Administration (2.4)]. (…) *Drug Interaction Studies* No specific drug interaction studies have been performed with ARISTADA. The drug interaction data provided below is obtained from studies with oral aripiprazole. Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cm ax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP 2D6 and CYP 3A4 inhibitors. After oral administration, a 3-fold increase in mean Cm ax and AUC values at steady-state is expected in poor metabolizers of CYP 2D6 administered with strong CYP 3A4 inhibitors. (See Figure 1, 2, and 3) *Specific Population Studies* A population pharmacokinetic analysis showed no effect of sex, race or smoking on ARISTADA pharmacokinetics [see Use in Specific Populations (8.8)]. 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)
021248, 06/20/2019	**Arsenic Trioxide**	Oncology	PML-RARA	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1. Newly-Diagnosed Low-Risk APL** TRISENOX is indicated in combination with tretinoin for treatment of adults with newlydiagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. **1.2. Relapsed or Refractory APL** TRISENOX is indicated for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. **14 CLINICAL STUDIES** **14.1 Newly-Diagnosed Low-Risk APL** (…) The trial enrolled 162 patients with a morphologic diagnosis of APL. The median age of patients was 45 years in the TRISENOX/tretinoin arm and 47 years in the chemotherapy/tretinoin arm, and 52% and 46% were male in the TRISENOX/tretinoin and chemotherapy/tretinoin arms, respectively. Baseline characteristics were balanced between treatment arms, including median WBC count, platelet count, PML-RARA isoform, and FLT3-ITD status. (…)
022466, 11/02/2018	**Articaine and Epinephrine (1)**	Anesthesiology	G6PD	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.4 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
022466, 11/02/2018	**Articaine and Epinephrine (2)**	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.4 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
761034, 05/06/2019	**Atezolizumab (1)**	Oncology	CD274 (PD-L1)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Urothelial Carcinoma** TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who: • are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD7 L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test [see Dosage and Administration (2.1)], or • are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or • have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. **1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer** TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on progression free survival [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection for Treatment of Urothelial Carcinoma and Triple-Negative Breast Cancer** Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with TECENTRIQ based on the PD-L1 expression on tumor infiltrating immune cells [see Clinical Studies (14.1)]. Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells [see Clinical Studies (14.3)].

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Last Updated: 06/2019

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					Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma or triple-negative breast cancer are available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Previously Treated Metastatic NSCLC* (…) The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see Clinical Studies (14.2)]. (…) **6.2 Immunogenicity** (…) Among 434 patients with TNBC in IMpassion130, 13% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 178 patients in PD-L1 positive subgroup with TNBC in IMpassion130, 12% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure [see Clinical Pharmacology (12.3)]. There are insufficient numbers of patients in the PD-L1 positive subgroup with ADA to determine whether ADA alters the efficacy of atezolizumab. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Specific Populations* Age (21–89 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 m), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST), level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab. (…) **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 119 patients, 27% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area). The remaining 73% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumor infiltrating IC covering < 5% of the tumor area). Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an ECOG PS of 2, 16% had a hearing loss ≥ 25 dB, and 9% had Grades 2-4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 14. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%). (See Table 14) (…) (…) Both cisplatin-eligible and cisplatin-ineligible patients are included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of <5% when treated with TECENTRIQ monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended closure of the monotherapy arm to further accrual of patients with low PD-L1 expression, however, no other changes were recommended for the study, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm. *Previously Treated Patients with Locally Advanced or Metastatic Urothelial Carcinoma* (…) Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5%. The remaining 68% of patients were classified as having PD-L1 expression of < 5%. Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 15. The median follow-up time for this study was 32.9 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 831 12.3%, 34.7%). (See Table 15) (…) **14.2 Non-Small Cell Lung Cancer** *Metastatic Chemotherapy-Naive Non-Squamous NSCLC* Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures. The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations.

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Last Updated: 06/2019

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					A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m2 while the remaining 87% received paclitaxel at a dose of 200 mg/m2 . Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC. The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 16 and Figure 1. (…) *Previously Treated Metastatic NSCLC* The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with locally advanced or metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disease, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppression within 2 weeks prior to enrollment were ineligible. Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. nonsquamous). Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. The major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PDL1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v.1.1. Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors. (See Table 17 and Figure 2) Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for prespecified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression. **14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer** (…) Patients were stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) (PD-L1 stained tumor-infiltrating immune cells [IC]<1% of tumor area vs. ≥ 1% of the tumor area) by the VENTANA PD-L1 (SP142) Assay. Of the 902 patients in the intent to treat population (ITT), 41% (369 patients) were classified as PD-L1 expression ≥ 1%. (…) **(…)** Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population. Tumor specimens (archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses. The major efficacy outcomes were investigator-assessed progression free survival (PFS) in the ITT and PD-L1 expressing patient population per RECIST v1.1 and overall survival (OS) in the ITT population. Overall survival data were immature with 43% deaths in the ITT population. The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 18 and Figure 3.
761034, 05/06/2019	**Atezolizumab (2)**	Oncology	Gene Signature (T-effector)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Non-Small Cell Lung Cancer** Metastatic Chemotherapy-Naive Non-Squamous NSCLC The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (tGE) status and ECOG performance status 0 or 1. (…) (…) Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures. The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITTWT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations. A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. (…)

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					(…) The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 16 and Figure 1. (…)
761034, 05/06/2019	**Atezolizumab (3)**	Oncology	EGFR	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 Non-Small Cell Lung Cancer** • TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations. • TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. **14 CLINICAL STUDIES** **14.2 Non-Small Cell Lung Cancer** Metastatic Chemotherapy-Naive Non-Squamous NSCLC The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 841 or T-effector gene (tGE) status and ECOG performance status 0 or 1. (…) **(…)** The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT- WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations. (…) **(…)** Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC. (…)
761034, 05/06/2019	**Atezolizumab (4)**	Oncology	ALK	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 Non-Small Cell Lung Cancer** • TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations. • TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. **14 CLINICAL STUDIES** **14.2 Non-Small Cell Lung Cancer** Metastatic Chemotherapy-Naive Non-Squamous NSCLC The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 841 or T-effector gene (tGE) status and ECOG performance status 0 or 1. (…) **(…)** The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT- WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations. (…) **(…)** Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC. (…)
021411, 05/19/2017	**Atomoxetine**	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.4 Dosing in Specific Populations** Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs. In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. **5 WARNINGS AND PRECAUTIONS** **5.12 Laboratory Tests** Routine laboratory tests are not required. CYP2D6 metabolism- Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory

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					tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA [see Adverse Reactions (6.1)]. **5.13 Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients who are known to be CYP2D6 PMs** Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4 hydroxyatomoxetine. Dosage adjustment of STRATTERA may be necessary when coadministered with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine) or when administered to CYP2D6 PMs. [See Dosage and Administration (2.4) and Drug Interactions (7.2)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Child and Adolescent Clinical Trials* (…) The following adverse reactions occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: insomnia (11% of PMs, 6% of EMs); weight decreased (7% of PMs, 4% of EMs); constipation (7% of PMs, 4% of EMs); depression (7% of PMs, 4% of EMs); tremor (5% of PMs, 1% of EMs); excoriation (4% of PMs, 2% of EMs); middle insomnia (3% of PMs, 1% of EMs); conjunctivitis (3% of PMs, 1% of EMs); syncope (3% of PMs, 1% of EMs); early morning awakening (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs); sedation (4% of PMs, 2% of EMs). (…) *Adult Clinical Trials* (…) The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metaboliser (EM) patients: vision blurred (4% of PMs, 1% of EMs); dry mouth (35% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs); feeling jittery (5% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (6% of PMs, 2% of EMs); hyperhidrosis (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of EMs). (…) **7 DRUG INTERACTIONS** **7.2 Effect of CYP2D6 Inhibitors on Atomoxetine** In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and Css, max is about 3- to 4-fold greater than atomoxetine alone. In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine. **8 USE IN SPECIFIC POPULATIONS** **8.6 Hepatic Insufficiency** Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (ChildPugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency [see Dosage and Administration (2.3)]. **8.7 Renal Insufficiency** EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen. **8.9 Ethnic Origin** Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians). **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The effect of STRATTERA on QTc prolongation was evaluated in a randomized, double-blinded, positive-(moxifloxacin 400 mg) and placebo-controlled, cross-over study in healthy male CYP2D6 poor metabolizers. A total of 120 healthy subjects were administered STRATTERA (20 mg and 60 mg) twice daily for 7 days. No large changes in QTc interval (i.e., increases >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*

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Last Updated: 06/2019

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					Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary [see Warnings and Precautions (5.13)]. Atomoxetine did not inhibit or induce the CYP2D6 pathway. The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs). Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N- desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours). (…)
021881, 12/07/2018	**Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate**	Gastroenterology	G6PD	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.8 Glucose-6-phosphate dehydrogenase (G-6-PD) Deficiency** Since MoviPrep contains sodium ascorbate and ascorbic acid, MoviPrep should be used with caution in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, especially G-6-PD deficiency patients with an active infection, with a history of hemolysis, or taking concomitant medications known to precipitate hemolytic reactions.
210238, 06/30/2019	**Avatrombopag (1)**	Hematology	F2 (Prothrombin)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210238, 06/30/2019	**Avatrombopag (2)**	Hematology	F5 (Factor V Leiden)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210238, 06/30/2019	**Avatrombopag (3)**	Hematology	PROC	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210238, 06/30/2019	**Avatrombopag (4)**	Hematology	PROS1	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

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Last Updated: 06/2019

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210238, 06/30/2019	**Avatrombopag (5)**	Hematology	SERPINC1 (Antithrombin III)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210238, 06/30/2019	**Avatrombopag (6)**	Hematology	CYP2C9	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** The CYP2C9*2 and CYP2C9*3 loss-of-function polymorphisms result in reduced CYP2C9 enzymatic activity. In a pooled pharmacogenomic analysis of avatrombopag studies, subjects heterozygous for CYP2C9 loss-of-function polymorphisms (intermediate metabolizers [n=24]) had approximately 1.4-fold higher exposure and subjects homozygous for CYP2C9 loss-of-function polymorphisms (poor metabolizers [n=2]) had approximately 2-fold higher exposure compared to subjects wild-type for CYP2C9 (normal metabolizers [n=94]).
761049, 05/14/2019	**Avelumab**	Oncology	CD274 (PD-L1)	Clinical Studies	**14 CLINICAL STUDIES** (…) A total of 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive (≥ 1% of tumor cells), 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 (MCV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCV. Efficacy results are presented in Table 8. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV.
016324, 12/20/2018	**Azathioprine (1)**	Rheumatology	TPMT	Dosage and Administration, Warnings, Precautions, Drug Interactions, Adverse Reactions, Clinical Pharmacology	**DOSAGE AND ADMINISTRATION** **Patients with TPMT and/or NUDT15 Deficiency** Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). *Homozygous deficiency in either TPMT or NUDT15* Because of the risk of increased toxicity, consider alternative therapies for patients who are known to have TPMT or NUDT15 deficiency (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). *Heterozygous deficiency in TPMT and/or NUDT15* Because of the risk of increased toxicity, dosage reduction is recommended in patients known to have heterozygous deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). **WARNINGS** *Cytopenias* *TPMT or NUDT15 Deficiency* (…) Patients with thiopurine S-methyl transferase (TPMT) or nucleotide diphospatase (NUDT15) deficiency may be at an increased risk of severe and life-threatening myelotoxicity if receiving conventional doses of IMURAN (see CLINCIAL PHARMACOLOGY). Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine. In patients with severe myelosuppression, consider evaluation for TPMT and NUDT15 deficiency (see PRECAUTIONS: Laboratory Tests). Consider alternative therapy in patients with homozygous TPMT or NUDT15 deficiency and reduced dosages in patients with heterozygous deficiency (see DOSAGE AND ADMINISTRATION). **PRECAUTIONS** ***TPMT and NUDT15 Testing:*** Consider genotyping or phenotyping patients for TPMT deficiency and genotyping for NUDT1 deficiency in patients with severe myelosuppression. TPMT and NUDT15 testing cannot substitute for complete blood count (CBC) monitoring in patients receiving IMURAN. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections). *Drug Interactions* Use with Allopurinol: One of the pathways for inactivation of azathioprine is inhibited by allopurinol. Patients receiving IMURAN and allopurinol concomitantly should have a dose reduction of IMURAN, to approximately 1/3 to 1/4 the usual dose. It is recommended that a further dose reduction or alternative therapies be considered for patients with low or absent TPMT activity receiving IMURAN and allopurinol because both TPMT and XO inactivation pathways are affected. See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS: Laboratory Tests and ADVERSE REACTIONS sections. **ADVERSE REACTIONS** *Hematologic* (…) Patients with low or absent TPMT or NUDT15 activity are at increased risk for severe, life-threatening myelosuppression from IMURAN (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias and PRECAUTIONS: Laboratory Tests, DOSAGE AND ADMINISTRATION).

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Last Updated: 06/2019

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					CLINICAL PHARMACOLOGY (…) 6-MP undergoes two major inactivation routes. One is thiol methylation, which is catalyzed by the enzyme thiopurine Smethyltransferase (TPMT), to form the inactive metabolite methyl-6-MP (6-MeMP). Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) to form 6-thiouric acid. The nucleotide diphosphatase (NUDT15) enzyme is involved in conversion of the 6-TGNs to inactive 6-TG monophosphates. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities. Genetic polymorphisms influence TPMT and NUDT15 activity. Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of 6-MP or azathioprine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. Because of the risk of toxicity, patients with TPMT or NUDT15 deficiency require alternative therapy or dose modification (see DOSAGE and ADMINISTRATION). Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. (…)
016324, 12/20/2018	Azathioprine (2)	Rheumatology	NUDT15	Dosage and Administration, Warnings, Precautions, Adverse Reactions, Clinical Pharmacology	**DOSAGE AND ADMINISTRATION** **Patients with TPMT and/or NUDT15 Deficiency** Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). *Homozygous deficiency in either TPMT or NUDT15* Because of the risk of increased toxicity, consider alternative therapies for patients who are known to have TPMT or NUDT15 deficiency (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). *Heterozygous deficiency in TPMT and/or NUDT15* Because of the risk of increased toxicity, dosage reduction is recommended in patients known to have heterozygous deficiency of TPMT or NUDT15. Patients who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, and PRECAUTIONS: Laboratory Tests). **WARNINGS** *Cytopenias* *TPMT or NUDT15 Deficiency* (…) Patients with thiopurine S-methyl transferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency may be at an increased risk of severe and life-threatening myelotoxicity if receiving conventional doses of IMURAN (see CLINCIAL PHARMACOLOGY). Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine. In patients with severe myelosuppression, consider evaluation for TPMT and NUDT15 deficiency (see PRECAUTIONS: Laboratory Tests). Consider alternative therapy in patients with homozygous TPMT or NUDT15 deficiency and reduced dosages in patients with heterozygous deficiency (see DOSAGE AND ADMINISTRATION). **PRECAUTIONS** ***TPMT and NUDT15 Testing:*** Consider genotyping or phenotyping patients for TPMT deficiency and genotyping for NUDT15 deficiency in patients with severe myelosuppression. TPMT and NUDT15 testing cannot substitute for complete blood count (CBC) monitoring in patients receiving IMURAN. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections). **ADVERSE REACTIONS** *Hematologic* (…) Patients with low or absent TPMT or NUDT15 activity are at increased risk for severe, life-threatening myelosuppression from IMURAN (see CLINICAL PHARMACOLOGY, WARNINGS: Cytopenias and PRECAUTIONS: Laboratory Tests, DOSAGE AND ADMINISTRATION). **CLINICAL PHARMACOLOGY** (…) The nucleotide diphosphatase (NUDT15) enzyme is involved in conversion of the 6-TGNs to inactive 6-TG monophosphates. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities. Genetic polymorphisms influence TPMT and NUDT15 activity. Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of 6-MP or azathioprine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. Because of the risk of toxicity, patients with TPMT or NUDT15 deficiency require alternative therapy or dose modification (see DOSAGE and ADMINISTRATION). Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of

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Last Updated: 06/2019

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					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. (…)
206256, 04/12/2017	Belinostat	Oncology	UGT1A1	Dosage and Administration, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.3 Patients with Reduced UGT1A1 Activity** Reduce the starting dose of Beleodaq to 750 mg/m2 in patients known to be homozygous for the UGT1A1*28 allele [see Clinical Pharmacology (12.5)]. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 20% of the black population, 10% of the white population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele. Additional reduced function alleles may be more prevalent in specific populations. Because belinostat is primarily (80-90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (e.g., patients with UGT1A1*28 allele). Reduce the starting dose of Beleodaq to 750 mg/m^2 in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities.
210498, 01/23/2019	Binimetinib (1)	Oncology	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating MEKTOVI [Clinical Studies (14)]. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics. **5 WARNINGS AND PRECAUTIONS** **5.3 Ocular Toxicities** *Retinal Vein Occlusion* RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 1 patient experienced RVO (0.1%). (…) **5.4 Interstitial Lung Disease** In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 2 patients (0.3%) developed interstitial lung disease (ILD), including pneumonitis. **5.6 Rhabdomyolysis** Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevation of laboratory values of serum CPK occurred in 58% of patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), rhabdomyolysis was reported in 1 patient (0.1%). (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data described in Warnings and Precautions [see Warnings and Precautions (5)] reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in a randomized open-label, activecontrolled trial (COLUMBUS) or, for rare events, exposure of 690 patients with BRAF V600 mutation- positive melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials. The data described below reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in COLUMBUS. (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** Of the 690 patients with BRAF mutation-positive melanoma who received MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of MEKTOVI plus encorafenib were observed in elderly patients as compared to younger patients [see Clinical Pharmacology (12.3)]. **14 CLINICAL STUDIES** MEKTOVI in combination with encorafenib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. (…) (…) Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (< 1%). (…)

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

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210498, 01/23/2019	**Binimetinib (2)**	Oncology	UGT1A1	Clinical Pharmacology	**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).
125557, 04/18/2019	**Blinatumomab**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Adverse Reactions, Clinical Studies	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL* The safety data described below reflect exposure to BLINCYTO in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO (n = 267) or standard of care (SOC) chemotherapy (n = 109). (…) **14 CLINICAL STUDIES** **14.1 MRD-positive B-cell Precursor ALL** *BLAST Study* Study 1 was an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic hematopoietic stem cell transplantation [HSCT], and had ≥ 10% blasts in bone marrow). (See Table 12) (…) **14.2 Relapsed/Refractory B-cell Precursor ALL** *TOWER Study* The efficacy of BLINCYTO was compared to standard of care (SOC) chemotherapy in a randomized, open-label, multicenter study (TOWER Study) [NCT02013167]. (See Table 15) (…) *Study MT103-211* Study MT103-211 [NCT01466179] was an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of alloHSCT, and had ≥ 10% blasts in bone marrow). (See Table 16) (…) *ALCANTARA Study* The efficacy of BLINCYTO for treatment of Philadelphia chromosome-positive B-cell precursor ALL was evaluated in an open-label, multicenter, single-arm study (ALCANTARA Study) [NCT02000427]. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-positive B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later tyrosine kinase inhibitor (TKI), or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate. (See Table 18) (…)
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 substudy population relative to the overall trial population. (See Table 9)
203341, 10/18/2018	**Bosutinib**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** BOSULIF is indicated for the treatment of adult patients with: • Newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial. • Chronic phase, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy. **2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dosing** The recommended dose is taken orally once daily with food. The tablet is to be swallowed whole and should not be broken or cut. Continue treatment with BOSULIF until disease progression or intolerance to therapy. If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual prescribed dose on the following day. Newly-Diagnosed CP Ph+ CML The recommended dose of BOSULIF is 400 mg orally once daily with food. CP, AP, or BP Ph+ CML with Resistance or Intolerance to Prior Therapy The recommended dose and schedule of BOSULIF is 500 mg orally once daily with food. 2.5 Dose Adjustments for Renal Impairment or Hepatic Impairment

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

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					The recommended starting doses for patients with renal and hepatic impairment are described in Table 2 below. (See Table 2) **5 WARNINGS AND PRECAUTIONS** **5.1 Gastrointestinal Toxicity** Diarrhea, nausea, vomiting, and abdominal pain occur with BOSULIF treatment. Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and fluid replacement. In the randomized clinical trial in patients with newly-diagnosed Ph+ CML, the median time to onset for diarrhea (all grades) was 3 days and the median duration per event was 3 days. (…) **5.4 Fluid Retention** Fluid retention occurs with BOSULIF and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. In the randomized clinical trial of 268 patients with newly-diagnosed CML in the bosutinib treatment group, 1 patient (0.4%) experienced severe fluid retention of Grade 3 pericardial effusion. Among 546 patients in a single-arm study in patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3 or 4 fluid retention was reported in 26 patients (5%). Some patients experienced more than one fluid retention event. Specifically, 21 patients experienced Grade 3 or 4 pleural effusions, 7 patients experienced Grade 3 or Grade 4 pericardial effusions, and 6 patients experienced Grade 3 edema. Monitor and manage patients using standards of care. Interrupt, dose reduce or discontinue BOSULIF as necessary [see Dosage and Administration (2.3) and Adverse Reactions (6)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Adverse Reactions in Patients With Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML* The single-arm clinical trial enrolled patients with Ph+ CP, AP, or BP CML and with resistance or intolerance to prior therapy [see Clinical Studies (14)]. The safety population (received at least 1 dose of BOSULIF) included 546 CML patients: (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** In the Phase 1/2 clinical trial of BOSULIF in patients with Ph+ CML, 20% were age 65 and over, 4% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **14 CLINICAL STUDIES** **14.1 Newly-Diagnosed CP Ph+ CML** The efficacy of BOSULIF in patients with newly-diagnosed chronic phase Ph+ CML was evaluated in the Bosutinib trial in First-line chrOnic myelogenous leukemia tREatment (BFORE) Trial: "A Multicenter Phase 3, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia" [NCT02130557]. The BFORE Trial is a 2-arm, open-label, randomized, multicenter trial conducted to investigate the efficacy and safety of BOSULIF 400 mg once daily alone compared with imatinib 400 mg once daily alone in adult patients with newly-diagnosed CP Ph+ CML. The trial randomized 536 patients (268 in each arm) with Ph+ or Ph- newly-diagnosed CP CML (intent-to-treat [ITT] population) including 487 patients with Ph+ CML harboring b2a2 and/or b3a2 transcripts at baseline and baseline BCR-ABL copies >0 (modified intent-to-treat [mITT] population). Randomization was stratified by Sokal score and geographical region. All patients are being treated and/or followed for up to 5 years. Efficacy was evaluated in the mITT population. The major efficacy outcome measure was MMR at 12 months defined as ≤0.1% BCR-ABL ratio on international scale (corresponding to ≥3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts as assessed by the central laboratory. Additional efficacy outcomes included CCyR by 12 months, defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable. (…) **14.2 Imatinib-Resistant or -Intolerant Ph+ CP, AP, and BP CML** Study 200 (NCT00261846), a single-arm, open-label, multicenter study in patients with CML who were resistant or intolerant to prior therapy was conducted to evaluate the efficacy and safety of BOSULIF 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for CP, AP, and BP disease previously treated with 1 prior TKI (imatinib) or more than 1 TKI (imatinib followed by dasatinib and/or nilotinib). (See Table 9) (…)
125388, 11/16/2018	**Brentuximab Vedotin (1)**	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; 26% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative. (…)
125388, 11/16/2018	**Brentuximab Vedotin (2)**	Oncology	TNFRSF8 (CD30)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** **1.4 Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), in combination with chemotherapy** ADCETRIS is indicated for the treatment of adult patients with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone. **1.6 Relapsed primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30- expressing mycosis fungoides (MF)** ADCETRIS is indicated for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy. **2 DOSAGE AND ADMINISTRATION**

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Last Updated: 06/2019

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					2.1 Recommended Dosage For dosing instructions of combination agents administered with ADCETRIS, see Clinical Studies (14.1 and 14.2) and the manufacturer's prescribing information. (See Table 1) **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** (…) Data summarizing ADCETRIS exposure are also provided for 347 patients with T-cell lymphoma, including 223 patients with PTCL who received ADCETRIS in combination with chemotherapy in a randomized, double-blind, controlled trial; 58 patients with sALCL who received ADCETRIS monotherapy in a single-arm trial; and 66 patients with pcALCL or CD30-expressing MF who received ADCETRIS monotherapy in a randomized, controlled trial. (…) *Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30- Expressing Peripheral T-Cell Lymphomas (Study 6, ECHELON-2)* ADCETRIS in combination with CHP was evaluated in patients with previously untreated, CD30- expressing PTCL in a multicenter randomized, double-blind, double dummy, actively controlled trial. (See Table 7) (…) *Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides (Study 4: ALCANZA)* ADCETRIS was studied in 131 patients with pcALCL or CD30-expressing MF requiring systemic therapy in a randomized, open-label, multicenter clinical trial in which the recommended starting dose and schedule was ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice of either methotrexate 5 to 50 mg orally weekly or bexarotene 300 mg/m2 orally daily. (See Table 9) (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** (…) In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHELON-2), 31% of ADCETRIS + CHP-treated patients were age 65 or older. (…) (…) In the clinical trial of ADCETRIS in pcALCL or CD30-expressing MF (Study 4: ALCANZA), 42% of ADCETRIS-treated patients were age 65 or older. No meaningful differences in safety or efficacy were observed between these patients and younger patients. **14 CLINICAL STUDIES** **14.2 Systemic Anaplastic Large Cell Lymphoma and Other CD30-Expressing Peripheral T-Cell Lymphomas** *Randomized Clinical Trial in Previously Untreated Systemic Anaplastic Large Cell Lymphoma or Other CD30-Expressing Peripheral T-Cell Lymphomas (Study 6: ECHELON-2, NCT01777152)* The efficacy of ADCETRIS in combination with chemotherapy for the treatment of adult patients with previously untreated, CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. For enrollment, the trial required CD30 expression ≥10% per immunohistochemistry. The trial excluded patients with primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. (See Table 13) (…) **14.4 Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-Expressing Mycosis Fungoides** *Randomized Clinical Trial in Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA, NCT01578499)* The efficacy of ADCETRIS in patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) requiring systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. (…) (…) Patients with pcALCL must have received prior radiation or systemic therapy, and must have at least 1 biopsy with CD30-expression of ≥10%. Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30- expression of ≥10% in at least 1 biopsy. A total of 131 patients were randomized (66 ADCETRIS, 65 physician's choice). The efficacy results were based on 128 patients (64 patients in each arm with CD30-expression of ≥10% in at least one biopsy). (See Table 15) (...) (…) Supportive trials include 2 single-arm trials, which enrolled patients with MF who were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Out of 73 patients with MF from the 2 pooled supportive trials, 34% (25/73) achieved ORR4. Among these 73 patients, 35 had 1% to 9% CD30-expression and 31% (11/35) achieved ORR4.
205422, 02/09/2018	**Brexpiprazole**	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.5 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inhibitors or Inducers** Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). If the coadministered drug is discontinued, adjust the REXULTI dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks [see Drug Interactions (7.1), Clinical Pharmacology (12.3)]. (See Table 1) **8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2D6 Poor Metabolizers** Dosage adjustment is recommended in known CYP2D6 poor metabolizers, because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Drug Interaction Studies*

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Last Updated: 06/2019

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					Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors [see Drug Interactions (7.1)].
208772, 12/21/2018	Brigatinib	Oncology	ALK	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** 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. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** (…) 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. (…) **14 CLINICAL STUDIES** The efficacy of ALUNBRIG was demonstrated in a two-arm, open-label, multicenter trial (ALTA, NCT02094573) in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib. The study required patients to have a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. (…)
205836, 05/12/2018	Brivaracetam	Neurology	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.
009386, 12/24/2003	Busulfan	Oncology	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies	**14 CLINICAL STUDIES** (…) Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph) chromosome. Also, the so-called “juvenile” type of chronic myelogenous leukemia, typically occurring in young children and associated with the absence of a Philadelphia chromosome, responds poorly to busulfan. The drug is of no benefit in patients whose chronic myelogenous leukemia has entered a “blastic” phase. (…)
203756, 01/12/2018	Cabozantinib	Oncology	RET	Clinical Studies	**14 CLINICAL STUDIES** (…) Of 330 patients randomized, 67% were male, the median age was 55 years, 23% were 65 years or older, 89% were white, 54% had a baseline ECOG performance status of 0, and 92% had undergone a thyroidectomy. The RET mutation status determined by a research use assay was positive in 51%, negative in 14%, and was unknown in 35%. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI. (…)
020896, 02/22/2019	Capecitabine	Oncology	DPYD	Warnings and Precautions, Patient Counseling Information	**5 WARNINGS AND PRECAUTIONS** **5.4 Dihydropyrimidine Dehydrogenase Deficiency** Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA. Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No XELODA dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test. **17 PATIENT COUNSELING INFORMATION** *Dihydropyrimidine Dehydrogenase 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)].
016608, 03/20/2018	Carbamazepine (1)	Neurology	HLA-B	Boxed Warning, Warnings, Precautions	**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

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					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.
016608, 03/20/2018	**Carbamazepine (2)**	Neurology	HLA-A	Warnings	**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 HLAA*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 (see 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. The risks and benefits of Tegretol therapy should be weighed before considering Tegretol in patients known to be positive for HLA A*3101. Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive and HLA-A*3101-positive patients treated with Tegretol will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B*1502-negative and HLA-A*3101 negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring, have not been studied.
022562, 11/16/2017	**Carglumic Acid**	Inborn Errors of Metabolism	NAGS	Indications and Usage, Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical	**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 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.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Pharmacology, Clinical Studies	**2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dosage** CARBAGLU should be initiated as soon as the diagnosis of NAGS deficiency is suspected, which may be as soon as at birth, and managed by a physician and medical team experienced in metabolic disorders. (…) **5 WARNINGS AND PRECAUTIONS** **5.1 Hyperammonemia** (…) Since hyperammonemia in NAGS deficiency is the result of imbalance between ammonia detoxification capacity and protein catabolism, complete protein restriction during an acute hyperammonemic episode is recommended for no longer than 12 to 36 hours while maximizing caloric supplementation to reverse catabolism. Protein should be reintroduced as early as possible, following improvement of metabolic and clinical abnormalities in this setting. During long-term management, dietary protein restriction should be instituted to maintain blood ammonia level within an acceptable range for age. **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 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 life-long for NAGS deficiency patients. **8.4 Pediatric Use** The efficacy of Carbaglu for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began 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 treatment with Carbaglu, a subset of 13 patients who had both well documented plasma ammonia levels prior to Carbaglu treatment and after long-term treatment with Carbaglu were selected for analysis. (…) (…) 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, 05/24/2019	**Cariprazine**	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINCIAL 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.
011792, 04/04/2019	**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 CLINCIAL 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*

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					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%.
020297, 09/14/2017	Carvedilol	Cardiology	CYP2D6	Drug Interactions, Clinical Pharmacology	**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 vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer. **12 CLINCIAL 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-mephenytoin (patients deficient in cytochrome P450 2C19).
020998, 05/03/2019	Celecoxib	Rheumatology	CYP2C9	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.7 Special Populations** *Poor Metabolizers of CYP2C9 Substrates* In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)]. **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see Poor Metabolizers of CYP2C9 substrates (8.8)]. **8.8 Poor Metabolizers of CYP2C9 Substrates** In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*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 *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.8)].
050585, 07/12/2018	Ceftriaxone (1)	Infectious Diseases	G6PD	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
050585, 07/12/2018	Ceftriaxone (2)	Infectious Diseases	Nonspecific (Congenital Methemoglobinemia)	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use (e.g. lidocaine). Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
205755, 03/05/2019	Ceritinib	Oncology	ALK	Indications and Usage, Dosage and Administration,	**1 INDICATIONS AND USAGE** ZYKADIA® is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Warnings and Precautions, Adverse Reactions, Clinical Studies	**2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics **5 WARNINGS AND PRECAUTIONS** Data in the Warnings and Precautions section reflect the safety of ZYKADIA 750 mg daily under fasted conditions in 925 patients with ALK-positive NSCLC across a pool of seven clinical studies at systemic exposures similar to the recommended dose of 450 mg with food. In a dose optimization study (ASCEND-8), there were no clinically meaningful differences observed in the incidence of toxicities described in Warnings and Precautions between patients receiving 750 mg daily under fasted conditions and 450 mg with food, except for a reduction in gastrointestinal adverse reactions as described [see Warnings and Precautions (5.1)]. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the Warnings and Precautions section reflect exposure to ZYKADIA 750 mg once daily in 925 patients with ALK-positive NSCLC across seven clinical studies, including ASCEND-4 and ASCEND-1, described below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies. (…) In ASCEND-8, a dose optimization study, ZYKADIA 450 mg daily with food (N = 89) was compared to 750 mg daily under fasted conditions (N = 90) in both previously treated and untreated patients with ALK-positive NSCLC. (…) *Previously Untreated ALK-Positive Metastatic NSCLC* The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study of 376 previously untreated ALK-positive NSCLC patients. Patients received ZYKADIA 750 mg daily (N=189) or chemotherapy plus maintenance chemotherapy (N=187). (…) *Previously Treated ALK-Positive Metastatic NSCLC* The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in ASCEND-1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily). (See Tables 5 and 6) (…) **14 CLINICAL STUDIES** **14.1 Previously Untreated ALK-Positive Metastatic NSCLC** The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ASCEND-4, NCT01828099). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. (…) **14.2 Previously Treated ALK-Positive Metastatic NSCLC** The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (ASCEND-1, NCT01283516). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily. (…) The study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastases included brain (60%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients. (…)
761052, 12/11/2018	**Cerliponase Alfa**	Inborn Errors of Metabolism	TPP1	Indications and Usage, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** Brineura is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** 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 peptidase 1 (TPP1) deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established. **14 CLINICAL STUDIES** The efficacy of Brineura was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency. (…) (…) Motor scores of the 22 Brineura-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study. The results of logistic modeling with covariates (screening age, screening

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					motor score, genotype: 0 key mutations (yes/no)), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% CI): 13.1 (1.2, 146.9)). (…) *Descriptive non-randomized comparison* (…) Given the non-randomized study design, a Cox Proportional Hazards Model adjusted for age, initial motor score, and genotype was used to evaluate time to unreversed 2-category decline or unreversed score of 0 in the Motor domain. This model showed a lesser decrease in motor function in the Brineura-treated patients when compared to the natural history cohort (see Figure 7). (…) *Motor Domain Scores: Matched Patients Only* (…) To further assess efficacy, the 22 patients from the Brineura clinical study with a baseline combined Motor plus Language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. Patients were matched based on the following covariates: baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening. (see Table 3) (…)
125084, 04/23/2019	**Cetuximab (1)**	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer** Erbitux is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use [see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Studies (14.2)]: • in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment, • in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. [See Warnings and Precautions (5.7), Clinical Pharmacology (12.1), Clinical Studies (14.2).] Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when he results of the Ras mutation tests are unknown [see Warnings and Precautions (5.7), Clinical Studies (14.2)]. **2 DOSAGE AND ADMINISTRATION** **2.2 Colorectal Cancer** Determine EGFR-expression status using FDA-approved tests prior to initiating treatment. Also confirm the absence of a Ras mutation prior to initiation of treatment with Erbitux. Information on FDA-approved tests for the detection of K-Ras mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/uc m301431.htm. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC) *In Combination with FOLFIRI* (…) The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…) *As Monotherapy* (…) The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)]. ERBITUX was administered intravenously at the recommended dosage (400 mg/m2 initial dose, followed by 250 mg/m2 weekly). Patients received a median of 17 infusions (range 1 to 51) [see Clinical Studies (14.2)]. (See Table 5) (…) In Combination with Irinotecan ERBITUX at the recommended dosage was administered in combination with irinotecan in 354 patients with EGFR expressing recurrent mCRC in Study CP02-9923 and BOND. (…) **14 CLINICAL STUDIES** **14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)** *In Combination with FOLFIRI* CRYSTAL (NCT00154102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive either a cetuximab product in combination with FOLFIRI or FOLFIRI alone as first-line treatment. Stratification factors were Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 versus 2) and region (Western Europe versus Eastern Europe versus other). (…) *As Monotherapy* Study CA225-025 (NCT00079066) was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent mCRC. (See Table 9) (…) *In Combination with Irinotecan* BOND was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. (…)
125084, 04/23/2019	**Cetuximab (2)**	Oncology	RAS	Indications and Usage, Dosage and Administration, Warnings and	**1 INDICATIONS AND USAGE** **1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer** Erbitux is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use [see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Studies (14.2)]: • in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment,

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Precautions, Adverse Reactions, Clinical Studies	• 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)]. **2 DOSAGE AND ADMINISTRATION** **2.2 Colorectal Cancer** Determine EGFR-expression status using FDA-approved tests prior to initiating treatment. Also confirm the absence of a Ras mutation prior to initiation of treatment with Erbitux. Information on FDA-approved tests for the detection of K-Ras mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/uc m301431.htm. **5 WARNINGS AND PRECAUTIONS** **5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC** Erbitux is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as "Ras" or when the Ras status is unknown. Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials including Study 4 were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. [See Indications and Usage (1.2), Clinical Pharmacology (12.1), Clinical Studies (14.2).] **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC) *In Combination with FOLFIRI* (…) The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. (See Table 4) (…) *As Monotherapy* The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)]. (See Table 5) (…) **14 CLINICAL STUDIES** **14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)** *In Combination with FOLFIRI* (…) K-Ras mutation status was available for 89% of the patients: 63% had K-Ras wild-type tumors and 37% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. Baseline characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population. (…) (…) Results of the planned PFS and ORR analysis in all randomized patients and post-hoc PFS and ORR analysis in subgroups of patients defined by K-Ras mutation status, and post-hoc analysis of updated OS based on additional followup (1000 events) in all randomized patients and in subgroups of patients defined by K-Ras mutation status are presented in Table 8 and Figure 2. The treatment effect in the all-randomized population for PFS was driven by treatment effects limited to patients who have K-Ras wild-type tumors. There is no evidence of effectiveness in the subgroup of patients with K-Ras mutant tumors. (See Table 8 and Figure 2) (…) (…) K-Ras status was available for 79% of the patients: 54% had K-Ras wild-type tumors and 46% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. (See Table 9 and Figure 3) (…) *In Combination with Irinotecan* BOND was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. (…)
020989, 12/08/2006	**Cevimeline**	Dental	CYP2D6	Precautions	**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, 10/24/2018	**Chloroquine**	Infectious Diseases	G6PD	Precautions, Adverse Reactions	**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. **ADVERSE REACTIONS** Blood and lymphatic system disorders: Pancytopenia, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia. Hemolytic anemia in G6PD deficient patients (see PRECAUTIONS).

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
011641, 02/01/2011	Chlorpropamide	Endocrinology	G6PD	Precautions	**PRECAUTIONS** *Hemolytic Anemia* Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because DIABINESE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.
009435, 11/02/2018	Chloroprocaine (1)	Anesthesiology	G6PD	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
009435, 11/02/2018	Chloroprocaine (2)	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
018057, 02/22/2019	Cisplatin	Oncology	TPMT	Adverse Reactions	**6 ADVERSE REACTIONS** *Ototoxicity* (…) Genetic factors (e.g., variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.
020822, 01/11/2019	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) **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. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION). CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.
020822, 01/11/2019	Citalopram (2)	Psychiatry	CYP2D6	Clinical Pharmacology	**CLINICAL PHARMACOLOGY** **Pharmacokinetics** *Population Subgroups* CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6. *Drug-Drug Interactions* Coadministration of a drug that inhibits CYP2D6 with Celexa is unlikely to have clinically significant effects on citalopram metabolism, based on the study results in CYP2D6 poor metabolizers.
202067, 06/15/2018	Clobazam	Neurology	CYP2C19	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers** In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 [see Use in Specific Populations (8.6), Clinical Pharmacology (12.5)]. **8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2C19 Poor Metabolizers** Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended [see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					12.3 Pharmacokinetics *Metabolism and Excretion* (…) The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethylclobazam [see Clinical Pharmacology (12.5)]. In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers. **12.5 Pharmacogenomics** The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethylclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethylclobazam 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 clobazam is similar for both CYP2C19 poor and extensive metabolizers.
019906, 05/10/2019	Clomipramine	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Drugs Metabolized by P450 2D6* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). (…)
020839, 05/17/2019	Clopidogrel	Cardiology	CYP2C19	Boxed Warning, Warnings and Precautions, Clinical Pharmacology	**BOXED WARNING** WARNING *Diminished antiplatelet effect in patients with two loss-of-function alleles of the CYP2C19 gene* The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. **5 WARNINGS AND PRECAUTIONS** **5.1 Diminished Antiplatelet Activity in Patients with Impaired CYP2C19 Function** Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 [see Boxed Warning]. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. Patients who are homozygous for nonfunctional alleles of the CYP2C19 gene are termed "CYP2C19 poor metabolizers". Approximately 2% of White and 4% of Black patients are poor metabolizers; the prevalence of poor metabolism is higher in Asian patients (e.g., 14% of Chinese). Tests are available to identify patients who are CYP2C19 poor metabolizers. A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. (See Table 3)
019758, 02/23/2017	Clozapine	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.7 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers** It may be necessary to reduce the CLOZARIL dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8.6, 8.7)]. **8 USE IN SPECIFIC POPULATIONS** **8.7 CYP2D6 Poor Metabolizers** Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted [see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *CYP2D6 Poor Metabolizers* A subset (3%–10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.
206192, 01/26/2018	Cobimetinib	Oncology	BRAF	Indications and Usage, Dosage	**1 INDICATIONS AND USAGE**

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Blue text represents the most recent addtions and/or changes since last posted version.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				and Administration, Adverse Reactions, Clinical Studies	COTELLIC® is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with COTELLIC with vemurafenib. Information on FDA approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The safety of COTELLIC was evaluated in Trial 1, a randomized (1:1), double blind, active-controlled trial in previously untreated patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma [see Clinical Studies (14)]. (…) **14 CLINICAL STUDIES** The safety and efficacy of cobimetinib was established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation test. (…) (…) The effect on PFS was also supported by analysis of PFS based on the assessment by blinded independent review. A trend favoring the cobimetinib with vemurafenib arm was observed in exploratory subgroup analyses of PFS, OS, and ORR in both BRAF V600 mutation subtypes (V600E or V600K) in the 81% of patients in this trial where BRAF V600 mutation type was determined.
022402, 09/18/2018	**Codeine**	Anesthesiology	CYP2D6	Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information	**BOXED WARNING** WARNING: ADDICTION, ABUSE, AND MISUSE; LIFETHREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism [see Warnings and Precautions (5.4)]. Codeine Sulfate Tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. Avoid the use of Codeine Sulfate Tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. (…) **5 WARNINGS AND PRECAUTIONS** **5.4 Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children** Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. (…) *Nursing Mothers* At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Codeine Sulfate Tablets [see Use in Specific Populations (8.2)]. *CYP2D6 Genetic Variability: Ultra-Rapid Metabolizers* Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)]. Therefore, individuals who are ultra-rapid metabolizers should not use Codeine Sulfate Tablets. **8 USE IN SPECIFIC POPULATIONS** **8.2 Lactation** *Risk Summary* Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Codeine Sulfate Tablets and any potential adverse effects on the breastfed infant from Codeine Sulfate Tablets or from the underlying maternal condition.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					8.4 Pediatric Use The safety and effectiveness of Codeine Sulfate Tablets in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received codeine [see Warnings and Precautions (5.4)]. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine. (…) **17 PATIENT COUNSELING INFORMATION** *Ultra-Rapid Codeine Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children* Advise caregivers that Codeine Sulfate Tablets are contraindicated in all 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 12 to 18 years of age receiving Codeine Sulfate Tablets to monitor for signs of respiratory depression [see Warnings and Precautions (5.4)].
202570, 06/25/2019	**Crizotinib (1)**	Oncology	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Clinical Studies (14.1, 14.2)]. Information on FDA-approved tests for the detection of ALK and ROS1 rearrangements in NSCLC is available at http://www.fda.gov/companiondiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm), 2, 3, a single arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154). The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3). (…) *Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014)* The data in Table 3 are derived from 340 patients with ALK-positive metastatic NSCLC who had not received previous systemic treatment for advanced disease who received treatment in a randomized, multicenter, open-label, active-controlled trial (Study 1). (…) *Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007)* The data in Table 5 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 2). (…) *ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001)* The safety profile of XALKORI from Study 3, which was evaluated in 50 patients with ROS1-positive metastatic NSCLC, was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC (n=1669). Vision disorders occurred in 92% of patients in Study 3; 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months. *Renal toxicity* The estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m2 (n=1681) to a median of 80.23 mL/min/1.73 m2 at 2 weeks (n=1499) in patients with ALK-positive advanced NSCLC who received XALKORI in clinical trials. (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. (…) **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac electrophysiology* In an ECG substudy conducted in 52 patients with ALK-positive NSCLC who received crizotinib 250 mg twice daily, the maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was 12.3 ms (2-sided 90% upper CI: 19.5 ms). An exposure-QT analysis suggested a crizotinib plasma concentration dependent increase in QTcF [see Warnings and Precautions (5.3)]. **14 CLINICAL STUDIES** **14.1 ALK-Positive Metastatic NSCLC** *Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014; NCT01154140)* The efficacy and safety of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active controlled study (Study 1). Patients were required to have ALK-positive

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Last Updated: 06/2019

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					NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit, prior to randomization. (See Table 7) (…) *Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007; NCT00932893)* The efficacy and safety of XALKORI as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum based chemotherapy regimen, were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). (…) (…) Patients were required to have ALK-positive NSCLC as identified by the FDA approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization. A total of 112 (64%) patients randomized to the chemotherapy arm subsequently received XALKORI after disease progression. (See Table 8) (…)
202570, 06/25/2019	**Crizotinib (2)**	Oncology	ROS1	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** XALKORI is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens [see Clinical Studies (14.1, 14.2)]. Information on FDA-approved tests for the detection of ALK and ROS1 rearrangements in NSCLC is available at http://www.fda.gov/companiondiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3). (…) *ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001)* The safety profile of XALKORI from Study 3, which was evaluated in 50 patients with ROS1-positive metastatic NSCLC, was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC (n=1669). Vision disorders occurred in 92% of patients in Study 3; 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months. **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical studies of XALKORI in patients with ROS1-positive metastatic NSCLC did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients. **14 CLINICAL STUDIES** **14.2 ROS1-Positive Metastatic NSCLC** *ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001; NCT00585195)* The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older, ECOG performance status of 0, 1, or 2, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRR and investigator, with imaging performed every 8 weeks for the first 60 weeks. Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (80%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. (See Table 9)
202806, 05/04/2018	**Dabrafenib (1)**	Oncology	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information	**ICATIONS AND USAGE** **1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma** TAFINLAR® is indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)]. **1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma** TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)]. **1.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma** TAFINLAR is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see Dosage and Administration (2.1), (2.3)]. **1.4 BRAF V600E Mutation-Positive Metastatic NSCLC**

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Last Updated: 06/2019

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					TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.4)]. **1.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer** TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)]. **1.6 Limitations of Use** TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC [see Warnings and Precautions (5.2)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Melanoma • Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent [see Warnings and Precautions (5.2) and Clinical Studies (14.1)]. • Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Warnings and Precautions (5.2), Clinical Studies (14.2), (14.3)]. • Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics. NSCLC • Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Clinical Studies (14.4)]. • Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics. **ATC** • Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib [see Clinical Studies (14.5)]. (…) **5 WARNINGS AND PRECAUTIONS** **5.2 Tumor Promotion in BRAF Wild-Type Melanoma** In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of TAFINLAR as a single agent or in combination with trametinib [see Indications and Usage (1.6), Dosage and Administration (2.1)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflect exposure to TAFINLAR administered as a single agent in 586 patients with various solid tumors and exposure to TAFINLAR administered with trametinib in 559 patients with melanoma and 93 patients with NSCLC. The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 300 mg). *Metastatic or Unresectable BRAF V600 Mutation Positive Melanoma* *TAFINLAR as a Single Agent* Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of the BREAK-3 study [see Clinical Studies (14.1)].This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m2 intravenously every 3 weeks (n = 63). (…) *TAFINLAR Administered with Trametinib* The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma who received TAFINLAR in two trials, Trial 2 (n = 209) a multicenter, double-blind, randomized (1:1), active controlled trial and Trial 3 (n = 350) a multicenter, open-label, randomized (1:1), active controlled trial. (…) *Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma* The safety of TAFINLAR when administered with trametinib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study [see Clinical Studies (14.3)]. (…) *Metastatic, BRAF V600E-Mutation Positive, Non-Small Cell Lung Cancer (NSCLC)* The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928). (…) *Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC)* The safety of TAFINLAR when administered with trametinib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). (…)

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Last Updated: 06/2019

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					12 CLINICAL PHARMACOLOGY **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The potential effect of TAFINLAR on QT prolongation was assessed in a dedicated multiple-dose study in 32 patients with BRAF V600 mutation-positive tumors. No large changes in the mean QT interval (i.e., >20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage). (…) **14 CLINICAL STUDIES** **14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent** In the BREAK-3 study (NCT01227889), the safety and efficacy of TAFINLAR as a single agent were demonstrated in an international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. (…) (…) All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were tested retrospectively, using an FDAapproved companion diagnostic test, THxID™-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 THxID™-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 12) (…) **14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR Administered with Trametinib** The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one openlabel 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 13 and Figures 2, 3) **14.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma** COMBI-AD (NCT 01682083) was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations as detected by the THxID™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or two placebos for up to 1 year. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable in-transit metastases, distant metastatic disease, or prior systemic anticancer treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIIa, IIIb, or IIIc). (…) (…) In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR in combination with trametinib and 432 to placebo. Median age was 51 years (range 18-89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 14) (…) **14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)** In Study BRF113928 (NCT01336634), the safety and efficacy of TAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK-inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). (…) (…) In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 15. (See Table 15) **14.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer (ATC)** The safety and efficacy of TAFINLAR administered with trametinib was evaluated in Study BRF117019 (NCT02034110), an activity estimating, nine-cohort, multi-center, non-randomized, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication; who received prior treatment with BRAF or MEK inhibitors; with symptomatic or untreated CNS metastases; or who had airway obstruction. (…)

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Last Updated: 06/2019

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					17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients of the following: Confirmation of BRAF V600 mutation • TAFINLAR as a single agent: Evidence of BRAF V600E mutation in the tumor specimen using an FDA-approved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)]. • • TAFINLAR with trametinib: Evidence of BRAF V600 mutation in tumor specimens using an FDAapproved test is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)]. (…)
202806, 05/04/2018	Dabrafenib (2)	Oncology	G6PD	Warnings and Precautions, Adverse Reactions, Patient Counseling Information	**5 WARNINGS AND PRECAUTIONS** **5.9 Glucose-6-Phosphate Dehydrogenase Deficiency** TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Metastatic or Unresectable BRAF V600E or V600K Mutation-Positive Melanoma *TAFINLAR as a Single Agent* Table 3 and Table 4 present adverse drug reactions identified from analyses of the BREAK-3 study [see Clinical Studies (14.1)]. This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m2 intravenously every 3 weeks (n = 63). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥ Grade 2), corrected QT interval greater than or equal to 480 milliseconds on electrocardiogram, or a known history of glucose-6-phosphate dehydrogenase deficiency. (…) **17 PATIENT COUNSELING INFORMATION** *Glucose-6-phosphate dehydrogenase (G6PD) deficiency* TAFINLAR may cause hemolytic anemia in patients with G6PD deficiency. Advice patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis [see Warnings and Precautions (5.9)].
202806, 05/04/2018	Dabrafenib (3)	Oncology	RAS	Dosage and Administration, Warnings and Precautions	**2 DOSAGE AND ADMINISTRATION** **2.3 Dose Modifications** *For New Primary Non-Cutaneous Malignancies* Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies. **5 WARNINGS AND PRECAUTIONS** **5.1 New Primary Malignancies** *Non-cutaneous Malignancies* Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. In the COMBI-d study, non-cutaneous malignancies occurred in 1.4% (3/209) of patients receiving TAFINLAR with trametinib and in 2.8% (6/211) of patients receiving single-agent TAFINLAR. In Study BRF113928, noncutaneous malignancies occurred in 1.1% (1/93) of patients receiving TAFINLAR with trametinib. Monitor patients receiving TAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies [see Dosage and Administration (2.3)].
206843, 11/09/2017	Daclatasvir	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Clinical Trials in HCV Genotype 3 (ALLY-3)** (…) The 152 treated subjects in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the subjects were male; 90% were white, 5% were Asian, and 4% were black. Most subjects (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype. SVR12 and outcomes in subjects without SVR12 in ALLY-3 are shown by patient population in Table 13. SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B allele status, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…) **14.3 Clinical Trials in HCV/HIV Coinfected Subjects (ALLY-2)** (…) Most subjects (80%) had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 16% of the subjects had compensated cirrhosis, and 73% had IL28B rs12979860 non-CC genotype. (…) (…) SVR12 rates were comparable regardless of antiretroviral therapy, HCV treatment history, age, race, gender, IL28B allele status, HCV genotype 1 subtype, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…) **14.4 Clinical Trials in Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Recurrence after Liver Transplantation (ALLY-1)** (…) Fifty-eight percent of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6, 77% had IL28B rs12979860 non-CC genotype. (…)

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					(…) SVR12 rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level. For SVR12 outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology (12.4). (…)
211288, 09/27/2018	**Dacomitinib**	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** VIZIMPRO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the first-line treatment of metastatic NSCLC with VIZIMPRO based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data in the Warnings and Precautions section reflect exposure to VIZIMPRO in 394 patients with first-line or previously treated NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations who received VIZIMPRO at the recommended dose of 45 mg once daily in 4 randomized, active-controlled trial [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), and Study A7471028 (N=16)] and one single-arm trial [Study A7471017 (N=30)]. The median duration of exposure to VIZIMPRO was 10.8 months (range 0.07-68) [see Warnings and Precautions (5)]. The data described below reflect exposure to VIZIMPRO in 227 patients with EGFR mutation-positive, metastatic NSCLC enrolled in a randomized, active-controlled trial (ARCHER 1050); 224 patients received gefitinib 250 mg orally once daily in the active control arm [see Clinical Studies (14)]. **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** Of the total number of patients (N=394) in five clinical studies with EGFR mutation-positive NSCLC who received VIZIMPRO at a dose of 45 mg orally once daily [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), Study A7471028 (N=16), and Study A7471017 (N=30)] 40% were 65 years of age and older. (…) **14 CLINICAL STUDIES** The efficacy of VIZIMPRO was demonstrated in a randomized, multicenter, multinational, open-label study (ARCHER 1050; [NCT01774721]). Patients were required to have unresectable, metastatic NSCLC with no prior therapy for metastatic disease or recurrent disease with a minimum of 12 months disease-free after completion of systemic therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; EGFR exon 19 deletion or exon 21 L858R substitution mutations. EGFR mutation status was prospectively determined by local laboratory or commercially available tests (e.g., therascreen® EGFR RGQ PCR and cobas® EGFR Mutation Test). Patients were randomized (1:1) to receive VIZIMPRO 45 mg orally once daily or gefitinib 250 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by region (Japanese versus mainland Chinese versus other East Asian versus non-East Asian), and EGFR mutation status (exon 19 deletions versus exon 21 L858R substitution mutation). (…) (…) Prognostic and tumor characteristics were ECOG performance status 0 (30%) or 1 (70%); 59% with exon 19 deletion and 41% with exon 21 L858R substitution; Stage IIIB (8%) and Stage IV (92%); 64% were never smokers; and 1% received prior adjuvant or neoadjuvant therapy. (…)
021794, 05/18/2018	**Dapsone (1)**	Dermatology	G6PD	Warnings and Precautions, Use in Specific Populations, Patient Counseling Information	**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** **8.2 Lactation Risk** Summary There is no information regarding the presence of topical dapsone in breastmilk, the effects on the breastfed infant, or the effects on milk production. Orally administered dapsone appears in human milk and could result in hemolytic anemia and hyperbilirubinemia especially in infants with G6PD deficiency. Systemic absorption of dapsone following topical application is minimal relative to oral dapsone administration; however, it is known that dapsone is present in human milk following administration of oral dapsone. **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

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

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					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. **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Patient Information). *Hematological Effects* • Inform patients that methemoglobinemia can occur with topical dapsone treatment. Advise patients to seek immediate medical attention if they develop cyanosis [see Warnings and Precautions (5.1)]. • Inform patients who have G6PD deficiency that hemolytic anemia may occur with topical dapsone treatment. Advise patients to seek medical attention if they develop signs and symptoms suggestive of hemolytic anemia [see Warnings and Precautions (5.2)].
021794, 05/18/2018	**Dapsone (2)**	Dermatology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions, Adverse Reactions, Patient Counseling Information	**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. **6 ADVERSE REACTIONS** **6.3 Postmarketing Experience** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use of topical dapsone: methemoglobinemia, rash (including erythematous rash, application site rash) and swelling of face (including lip swelling, eye swelling). **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Patient Information). *Hematological Effects* • Inform patients that methemoglobinemia can occur with topical dapsone treatment. Advise patients to seek immediate medical attention if they develop cyanosis [see Warnings and Precautions (5.1)]. • Inform patients who have G6PD deficiency that hemolytic anemia may occur with topical dapsone treatment. Advise patients to seek medical attention if they develop signs and symptoms suggestive of hemolytic anemia [see Warnings and Precautions (5.2)].
086841	**Dapsone (3)**	Infectious Diseases	G6PD	Precautions, Adverse Reactions, Overdosage	Labeling not electronically available on Drugs@FDA
021513, 03/15/2012	**Darifenacin**	Urology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Electrophysiology* The effect of six-day treatment of 15 mg and 75 mg Enablex on QT/QTc interval was evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44 percent male, 56 percent female) aged 18 to 65. Subjects included 18 percent poor metabolizer (PMs) and 82 percent extensive metabolizer (EMs). The QT interval was measured over a 24-hour period both predosing and at steady-state. The 75 mg Enablex dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, Enablex did not result in QT/QTc interval prolongation at any time during the 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*

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Last Updated: 06/2019

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					After oral administration of Enablex to healthy volunteers, peak plasma concentrations of darifenacin are reached approximately seven hours after multiple dosing and steady-state plasma concentrations are achieved by the sixth day of dosing. The mean (SD) steady-state time course of Enablex 7.5 mg and 15 mg extended-release tablets is depicted in Figure 1. A summary of mean (standard deviation, SD) steady-state pharmacokinetic parameters of Enablex 7.5 mg and 15 mg extended-release tablets in EMs and PMs of CYP2D6 is provided in Table 3. The mean oral bioavailability of Enablex in EMs at steady-state is estimated to be 15 percent and 19 percent for 7.5 mg and 15 mg tablets, respectively. (See Figure 1 and Table 3) *Variability in Metabolism* A subset of individuals (approximately 7 percent Caucasians and 2 percent African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM versus EM) for Cmax and AUC following darifenacin 15 mg once daily at steadystate 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 steadystate and co-administered with the potent CYP3A4 inhibitor ketoconazole 400 mg, mean darifenacin Cmax increased to 11.2 ng/mL for EMs (n = 10) and 55.4 ng/mL for one PM subject (n = 1). Mean AUC increased to 143 and 939 ng•h/mL for EMs and for one PM subject, respectively. When a 15 mg daily dose of Enablex was given with ketoconazole, mean darifenacin Cmax increased to 67.6 ng/mL and 58.9 ng/mL for EMs (n = 3) and one PM subject (n = 1), respectively. Mean AUC increased to 1110 and 931 ng•h/mL for EMs and for one PM subject, respectively [see Dosage and Administration (2) and Drug Interactions (7.1)].
206619, 07/23/2018	**Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir**	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis** *Subjects with Chronic HCV GT1a Infection without Cirrhosis* Subjects with HCV GT1a infection without cirrhosis treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV [see Clinical Studies (14.1)] had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 19% had a body mass index of at least 30 kg per m^2; 55% of patients were enrolled in US sites; 72% had IL28B (rs12979860) non-CC genotype; 85% had baseline HCV RNA levels of at least 800,000 IU per mL. (…) *Subjects with Chronic HCV GT1b Infection without Cirrhosis* Subjects with HCV GT1b infection without cirrhosis were treated with VIEKIRA PAK with or without RBV for 12 weeks in PEARL-II and -III [see Clinical Studies (14.1)]. Subjects had a median age of 52 years (range: 22 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were Hispanic or Latino; 21% had a body mass index of at least 30 kg per m^2; 21% of patients were enrolled in US sites; 83% had IL28B (rs12979860) nonCC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per mL. (…) **14.3 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection and Compensated Cirrhosis** (…) Treated subjects had a median age of 58 years (range: 21 to 71); 70% of the subjects were male; 95% were White; 3% were Black/African American; 12% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m^2; 43% of patients were enrolled in US sites; 82% had IL28B (rs12979860) non-CC genotype; 86% had baseline HCV RNA levels of at least 800,000 IU per mL; 69% had HCV GT1a infection, 31% had HCV GT1b infection; 42% were treatment-naïve, 36% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 14% were prior pegIFN/RBV relapsers; 15% had platelet counts of less than 90 x 10^9 per L; 50% had albumin less than 4.0 mg per dL. (…) (…) TURQUOISE-III was an open-label trial that enrolled 60 HCV GT1b-infected subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Subjects received VIEKIRA PAK without RBV for 12 weeks. Treated subjects had a median age of 61 years (range: 26 to 78); including 45% treatment-naïve and 55% pegIFN/RBV treatment-experienced; 25% were ≥65 years; 62% were male; 12% were Black; 5% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m^2; 40% of patients were enrolled in US sites; 22% had platelet counts of less than 90 x 10^9 per L; 17% had albumin less than 35 g/L; 92% had baseline HCV RNA levels of at least 800,000 IU per mL; 83% had IL28B (rs12979860) non-CC genotype. (…) **14.6 Clinical Trial in Subjects with HCV/HIV-1 Co-infection (TURQUOISE-I)** (…) Treated subjects had a median age of 51 years (range: 31 to 69); 24% of subjects were black; 81% of subjects had IL28B (rs12979860) non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection. (…)
021986, 12/21/2018	**Dasatinib**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific	**1 INDICATIONS AND USAGE** SPRYCEL (dasatinib) is indicated for the treatment of adults with • newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. • chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. • Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients 1 year of age and older with • Ph+ CML in chronic phase. • newly diagnosed Ph+ ALL in combination with chemotherapy.

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

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				Populations, Clinical Studies	**2 DOSAGE AND ADMINISTRATION** **2.1 Dosage of SPRYCEL in Adult Patients** The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening. **2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL** The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary. (See Table 1) Refer to Section 2.4 for recommendations on dose escalation in adults with CML and Ph+ ALL, and pediatric patients with CML. **2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML** For adult patients with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2 below). Dose escalation is not recommended for pediatric patients with Ph+ ALL, where SPRYCEL is administered in combination with chemotherapy. Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients with chronic phase CML who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. (See Tables 2, 3, and 4) **2.5 Dose Adjustment for Adverse Reactions** *Myelosuppression* (…) For pediatric patients with Ph+ ALL, if neutropenia and/or thrombocytopenia result in a delay of the next block of treatment by more than 14 days, interrupt SPRYCEL and resume at the same dose level once the next block of treatment is started. (…) Non-Hematologic Adverse Reactions For adults with Ph+ CML and ALL, and pediatric patients with Ph+ CML, if a severe nonhematologic adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event [see Warnings and Precautions (5.1)]. For pediatric patients with Ph+ ALL, interrupt treatment for cases of grade > 3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade <1. (…) **2.6 Duration of Treatment** In clinical studies, treatment with SPRYCEL in adults and in pediatric patients with chronic phase CML was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response [CCyR]) or major molecular response (MMR and MR4.5) has not been established. In clinical studies, treatment with SPRYCEL in pediatric patients with Ph+ ALL was administered for a maximum duration of 2 years [see Dosage and Administration (2.2) and Clinical Studies (14.4)]. SPRYCEL is an antineoplastic product. Follow applicable special handling and disposal procedures. **5 WARNINGS AND PRECAUTIONS** **5.1 Myelosuppression** Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML. In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated. (…) In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery. (…) **5.2 Bleeding-Related Events** In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction in vitro. In all CML or Ph+ ALL clinical studies, ≥grade 3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. Grade 3 or greater gastrointestinal hemorrhage, including fatalities, occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of ≥grade 3 hemorrhage occurred in 2% of patients. Most bleeding events in clinical studies were associated with severe thrombocytopenia. Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage. **5.3 Fluid Retention** (…) In patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural effusion reported in 7% of patients. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data described below reflect exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and 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 1618

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					SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation were reported in 329 (20.3%) patients; among the 1094 SPRYCEL treated patients with advanced phase CML or Ph+ ALL, drug-related adverse events leading to discontinuation were reported in 191 (17.5%) patients. (…) **Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults** A total of 135 patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. (…) Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients The safety of SPRYCEL administered continuously in combination with multiagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL. [see Clinical Studies (14.4)]. The median duration of therapy was 24 months (range 2 to 27 months). (See Tables 14 and 15) (…) **6.2 Additional Pooled Data From Clinical Trials** The following additional adverse reactions were reported in patients in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These events are included on the basis of clinical relevance. **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** Ph+ CML in Chronic Phase The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML [see Clinical Studies (14.3)]. There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of patients [see Warnings and Precautions (5.10)]. Ph+ ALL The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported. The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects [see Adverse Reactions (6.1) and Clinical Studies (14.3, 14.4)]. Monitor bone growth and development in pediatric patients [see Warnings and Precautions (5.10)]. Pediatric Patients with Difficulty Swallowing Tablets Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. (…) **14 CLINICAL STUDIES** (…) BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L, and V299L. Dasatinib does not appear to be active against the T315I mutation, based on in vitro data. **14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults** The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a 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 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL). *Advanced Phase CML and Ph+ ALL* Dose-Optimization Trial: One randomized open-label trial was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. (See Table 19) (…) (…) In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The 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: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively. **14.4 Ph+ ALL in Pediatric Patients** The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a single cohort (cohort 1) of Study CA180372 (NCT01460160), a multicenter, multiple-cohort study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. The 78 patients in cohort 1 received SPRYCEL at a daily dose of 60 mg/m2 for up to 24 months, in combination with chemotherapy. The backbone chemotherapy regimen was the AIEOP-BFM ALL 2000 multi-agent chemotherapy protocol. (…)
103767, 02/15/2019	**Denileukin Diftitox**	Oncology	IL2RA (CD25 antigen)	Indications and Usage, Warnings and Precautions, Clinical Studies	**1 INDICATIONS AND USAGE** Ontak is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the Il-2 receptor [see Warnings and Precautions (5.4)]. **5 WARNINGS AND PRECAUTIONS**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					5.4 CD25 Tumor Expression and Evaluation Confirm that the patient's malignant cells expressCD25 prior to administration of Ontak. A testing service for the assay of CD25 expression in tumor biopsy samples is available. **14 CLINICAL STUDIES** **14.1 Study 1: Placebo Controlled Study in CTCL (Stage 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 (CDI22/CD132). (…)
014399, 11/09/2018	**Desipramine**	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Drug Interactions* *Drugs Metabolized by P450 2D6.* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 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). (…)
020118, 03/01/2019	**Desflurane**	Anesthesiolgy	Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)	Contraindications	**4 CONTRAINDICATIONS** The use of SUPRANE is contraindicated in the following conditions: • Known or suspected genetic susceptibility to malignant hyperthermia. (…)
021992, 02/06/2018	**Desvenlafaxine**	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and elimination* Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. (…)
208082, 06/06/2018	**Deutetrabenazine**	Neurology	CYP2D6	Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers** In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Use in Specific Populations (8.7)]. **5 WARNINGS AND PRECAUTIONS** **5.7 QTc Prolongation** (…) A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizersor are co-administered a strong CYP2D6 inhibitor [see Clinical Pharmacology (12.2, 12.3)]. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary *[see Dosage and Administration (2.3, 2.4)]*. The use of AUSTEDO in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongations *[see Drug Interactions (7.2)]*. (...) **8 USE IN SPECIFIC POPULATIONS** **8.7 Poor CYP2D6 Metabolizers** Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similarly to taking a strong CYP2D6 inhibitor (approximately 3-fold). In patients who are CYP2D6 poor metabolizers, the daily dose of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Poor CYP2D6 Metabolizers* Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (approximately 3-fold) [see Dosage and Administration (2.4), Drug Interactions (7.1)].

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Last Updated: 06/2019

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022287, 06/07/2018	Dexlansoprazole	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* (…) CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates: extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). 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 the exposure to clopidogrel active metabolite. The effect on exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important. **12.5 Pharmacogenomics** *Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole* Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of DEXILANT 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.
021879, 06/11/2019	Dextromethorphan and Quinidine	Neurology	CYP2D6	Warnings and Precautions, Clinical Pharmacology	**5 WARNINGS AND PRECAUTIONS** **5.4 Concomitant use of CYP2D6 Substrates** The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 [see Drug Interactions (7.5)]. **5.8 CYP2D6 Poor Metabolizers** The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3), (12.5)]. Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluate in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover thorough QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for dextromethorphan 30 mg/quinidine 10 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype. **12.3 Pharmacokinetics** *Metabolism and Excretion* NUEDEXTA is a combination product containing dextromethorphan and quinidine. Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. After dextromethorphan 30mg/quinidine 30mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours. (…) **12.5 Pharmacogenomics** The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7-10% of Caucasians and 3-8% of African Americans generally lack the capacity to metabolize CYP2D6 substrates and are classified as PMs. The quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA [see Warnings and Precautions (5.4),(5.8), and Clinical Pharmacology (12.3)].

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

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020648, 12/16/2016	Diazepam	Neurology	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and Elimination* (…) The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are "poor metabolizers") and CYP3A4. (…)
125516, 03/01/2017	Dinutuximab	Oncology	MYCN	Clinical Studies	**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. (…)
022234, 09/24/2018	Docetaxel	Oncology	ESR, PGR (Hormone Receptor)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Adjuvant Treatment of Breast Cancer** **(…)** Docetaxel was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC. (See Table 14) (…)
204790, 09/06/2018	Dolutegravir	Infectious Diseases	UGT1A1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and Elimination* Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).
020690, 12/18/2018	Donepezil	Neurology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. Examination of the effect of CYP2D6 genotype in Alzheimer's patients showed differences in clearance values among CYP2D6 genotype subgroups. When compared to the extensive metabolizers, poor metabolizers had a 31.5% slower clearance and ultra-rapid metabolizers had a 24% faster clearance.
022036, 03/17/2010	Doxepin (1)	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5. Special Population** *Poor Metabolizers of CYPs* Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.
022036, 03/17/2010	Doxepin (2)	Psychiatry	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5. Special Population** *Poor Metabolizers of CYPs* Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.
205525, 09/14/2018	Dronabinol	Gastroenterology	CYP2C9	Use in Specific Populations, Clinical Pharmacology	**8 USE IN SPECIFIC POPULATIONS** **8.6 Effect of CYP2C9 Polymorphism** Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function [see Clinical Pharmacology (12.5)]. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Published data indicate a 2- to 3-fold higher dronabinol exposure in individuals carrying genetic variants associated with diminished CYP2C9 function.
021676, 08/09/2017	Drospirenone and Ethinyl Estradiol	Gynecology	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Effects of Combined Oral Contraceptives on Other Drugs* (…) In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. (…)
021427, 12/19/2017	Duloxetine	Psychiatry	CYP2D6	Drug Interactions	**7 DRUG INTERACTIONS** **7.3 Dual Inhibition of CYP1A2 and CYP2D6** Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
761069, 02/16/2018	Durvalumab	Oncology	CD274 (PD-L1)	Clinical Pharmacology, Clinical Studies	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Specific Populations* Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance (CLcr) 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status had no clinically significant effect on the pharmacokinetics of durvalumab. (…) **14 CLINICAL STUDIES** **14.1 Urothelial Carcinoma** (…) Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and immune cells (IC) at a central laboratory using the VENTANA PD-L1 (SP263) Assay. Of the 182 patients, 95 were classified as PD-L1 high (if ICs involve >1% of the tumor area, TC ≥25% or IC ≥25%; if ICs involve ≤1% of the tumor area, TC ≥25% or IC=100%), 73 as PD-L1 low/negative (did not meet criterion for PD-L1 high), and samples for 14 patients were not evaluable. (see Table 6) (…)
211155, 09/24/2018	Duvelisib	Oncology	Chromosome 17p	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Efficacy in Relapsed or Refractory CLL/SLL** Study 1 (…) In this subset (95 randomized to COPIKTRA, 101 to ofatumumab), the median patient age was 69 years (range: 40 to 90 years), 59% were male, and 88% had an ECOG performance status of 0 or 1. Forty-six percent received 2 prior lines of therapy, and 54% received 3 or more prior lines. At baseline, 52% of patients had at least one tumor ≥ 5 cm, and 22% of patients had a documented 17p deletion. (…)
020972, 10/10/2017	Efavirenz	Infectious Diseases	CYP2B6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The effect of SUSTIVA on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-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)].
210450, 07/23/2018	Elagolix	Gynecology	SLCO1B1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Disposition of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in groups of patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C). The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. Subjects with this genotype are expected to have a 78% mean increase in elagolix concentrations compared to subjects with normal transporter function (i.e., SLCO1B1 521T/T genotype).
208261, 06/28/2018	Elbasvir and Grazoprevir	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE COINFECTION)** (…) C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naïve subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized in a 3:1 ratio to: ZEPATIER for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with ZEPATIER for 12 weeks (deferred treatment group). Among subjects with genotype 1 infection randomized to the immediate treatment group, the median age was 55 years (range: 20 to 78); 56% of the subjects were male; 61% were White; 20% were Black or African American; 8% were Hispanic or Latino; mean body mass index was 26 kg/m^2 ; 72% had baseline HCV RNA levels greater than 800,000 IU per mL; 24% had cirrhosis; 67% had non-C/C IL28B alleles (CT or TT); and 55% had genotype 1a and 45% had genotype 1b chronic HCV infection. C-EDGE COINFECTION was an open-label, single-arm trial in treatment-naïve HCV/HIV-1 coinfected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks. Among subjects with genotype 1 infection, the median age was 50 years (range: 21 to 71); 85% of the subjects were male; 75% were White; 19% were Black or African American; 6% were Hispanic or Latino; mean body mass index was 25 kg per m^2 ; 59% had baseline HCV RNA levels greater than 800,000 IU per mL; 16% had cirrhosis; 65% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (…) **14.3 Clinical Trials in Treatment-Experienced Subjects with Genotype 1** HCV *Treatment-Experienced Subjects who Failed Prior PegIFN with RBV Therapy (C-EDGE TE)* (…) C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1 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/m^2 ; 78% had baseline HCV RNA levels greater than 800,000 IU/mL; 34% had cirrhosis; 79% had non-C/C IL28B alleles (CT or TT); and 60% had genotype 1a, 39% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection. (…) *Treatment-Experienced Subjects who Failed Prior PegIFN + RBV + HCV Protease Inhibitor Therapy (CSALVAGE)* C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					had a median age of 55 years (range: 23 to 75); 58% of the subjects were male; 97% were White; 3% were Black or African American; 15% were Hispanic or Latino; mean body mass index was 28 kg/m^2; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; and 97% had non-C/C IL28B alleles (CT or TT); 46% had baseline NS3 resistance-associated substitutions. Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions [see Microbiology (12.4)]. (…) **14.4 Clinical Trial in Subjects with Genotype 1 HCV and Severe Renal Impairment including Subjects on Hemodialysis (C-SURFER)** C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m^2) or CKD Stage 5 (eGFR<15 mL/min/1.73m^2), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or 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 for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR + GZR for 12 weeks (deferred treatment group). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive pharmacokinetic [PK] group). Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; and 72% had non-C/C IL28B alleles (CT or TT). Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 15.
205494, 08/29/2018	Eliglustat	Inborn Errors of Metabolism	CYP2D6	Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test [see Dosage and Administration (2.1)]. Limitations of Use: • Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect [see Clinical Studies (14)]. • A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) [see Clinical Studies (14)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients with Gaucher disease type 1 based on their CYP2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype [see Indications and Usage (1)]. **2.2 Recommended Adult Dosage** The recommended dosage of CERDELGA in adults is based on the patient's CYP2D6 metabolizer status. (See Table 1) **2.3 Dosage Adjustment in EMs and IMs With or Without Hepatic Impairment and Concomitant Use of CYP2D6 or CYP3A Inhibitors** Reduce dosage frequency of CERDELGA 84 mg to once daily in CYP2D6 EMs and IMs with or without hepatic impairment taking CYP2D6 or CYP3A inhibitors, as shown in Table 2 [see Warnings and Precautions (5.1), Drug Interactions (7.1), Use in Specific Populations (8.7)]. (See Table 2) **4 CONTRAINDICATIONS** CERDELGA is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals. EMs • Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [see Drug Interactions (7.1)] • Moderate or severe hepatic impairment [see Use in Specific Populations (8.7)] • Mild hepatic impairment and taking a strong or moderate CYP2D6 inhibitor [see Use in Specific Populations (8.7)] IMs • Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [see Drug Interactions (7.1)] • Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)] • Any degree of hepatic impairment [see Use in Specific Populations (8.7)] PMs • Taking a strong CYP3A inhibitor [see Drug Interactions (7.1)] • Any degree of hepatic impairment [see Use in Specific Populations (8.7)] **5 WARNINGS AND PRECAUTIONS** **5.1 ECG Changes and Potential for Cardiac Arrhythmias** CERDELGA is predicted to cause increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations and may increase the risk of cardiac arrhythmias. • Use of CERDELGA is contraindicated, to be avoided, or requires dosage adjustment in patients taking CYP2D6 or CYP3A inhibitors, depending CYP2D6 metabolizer status, type of inhibitor, or degree of hepatic impairment [see Dosage and Administration (2.3), Contraindications (4), Drug Interactions (7.1)]. (…))] **7 DRUG INTERACTIONS** **7.1 Effect of Other Drugs on CERDELGA**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					Coadministration of CERDELGA with: • CYP2D6 or CYP3A inhibitors may increase eliglustat concentrations which may increase the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac interval [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. • strong CYP3A inducers decreases eliglustat concentrations which may reduce CERDELGA efficacy [see Clinical Pharmacology (12.3)]. See Table 5 for prevention and management of interactions with drugs affecting CERDELGA. Use of CERDELGA is contraindicated, to be avoided, or may require dosage adjustment depending on the concomitant drug and CYP2D6 metabolizer status [see Dosage and Administration (2.2, 2.3), Contraindications (4), Drug Interactions (7.1)]. (See Tale 5) **8 USE IN SPECIFIC POPULATIONS** **8.6 Renal Impairment** Use CERDELGA in patients with renal impairment based on the patient's CYP2D6 metabolizer status [see Clinical Pharmacology (12.3)]. EMs • Avoid CERDELGA in patients with end-stage renal disease (ESRD) (estimated creatinine clearance (eCLcr) less than 15 mL/min not on dialysis or requiring dialysis). • No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment (eCLcr at least 15 mL/min). IMs and PMs • Avoid CERDELGA in patients with any degree of renal impairment. **8.7 Hepatic Impairment** Use CERDELGA in patients with hepatic impairment based on CYP2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors [see Clinical Pharmacology (12.3)]. EMs • CERDELGA is contraindicated in patients with [see Contraindications (4)]: o severe (Child-Pugh Class C) hepatic impairment o moderate (Child-Pugh Class B) hepatic impairment o mild (Child-Pugh Class A) hepatic impairment taking a strong or moderate CYP2D6 inhibitor • Reduce dosage frequency of CERDELGA 84 mg to once daily [see Dosage and Administration (2.3)] in patients with mild hepatic impairment taking: o a weak CYP2D6 inhibitor o a strong, moderate, or weak CYP3A inhibitor • No dosage adjustment is recommended in patients with mild hepatic impairment, unless otherwise specified above. IMs and PMs • CERDELGA is contraindicated in patients with any degree of hepatic impairment [see Contraindications (4)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Absorption The oral bioavailability of eliglustat was less than 5% in CYP2D6 EMs following a single 84 mg dose of CERDELGA. In CYP2D6 EMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose-proportional manner over the dose range of 42 to 294 mg (0.5 to 3.5 times the recommended dosage). In addition, after multiple oral doses of 84 mg twice daily in EMs, eliglustat systemic exposure (AUC0-12) increased up to about 2-fold at steady state compared to after the first dose (AUC0-∞). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7-fold to 9-fold higher in PMs. Dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted Cmax and AUC0-24hr in PMs using a physiologically based pharmacokinetic (PBPK) model with 84 mg once daily were 75 ng/mL and 956 hr·ng/mL, respectively. Table 7 describes the pharmacokinetic parameters for eliglustat in healthy subjects following multiple doses of 84 mg CERDELGA twice daily. (See Table 7) Administration of CERDELGA with a high fat meal (approximately 1000 calories with 50% calories from fat) resulted in a 15% decrease in Cmax (not clinically significant) but no change in AUC. Distribution Following intravenous administration, the volume of distribution of eliglustat was 835 L in EMs. Plasma protein binding of eliglustat ranges from 76% to 83%. Elimination Eliglustat terminal elimination half-life was approximately 6.5 hours in CYP2D6 EMs, and 8.9 hours in PMs. Following intravenous administration of 42 mg (0.5 times the recommended oral dose) in healthy subjects, the mean (range) of eliglustat total body clearance was 88 L/h (80 to 105 L/h) in EMs. Specific Populations No clinically significant differences in the pharmacokinetics of eliglustat were observed based on age (18 to 71 years), sex, race (mostly were Caucasian, including those of Ashkenazi Jewish descent; however, it included the following populations: African American, American Indians, Hispanics, and Asians), or body weight (41 to 136 kg). Patients with renal impairment Eliglustat pharmacokinetics was similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs. Eliglustat pharmacokinetics in EMs with ESRD and in IMs or PMs with any degree of renal impairment is unknown [see Use in Specific Populations (8.6)]. Patients with hepatic impairment Table 8 describes the effect of mild and moderate hepatic impairment on the pharmacokinetics of eliglustat in CYP2D6 EMs compared to EMs with normal hepatic function following a single 84 mg dose. The effect of hepatic impairment is highly variable with the coefficients of variation (CVs%) of 135% and 110% for Cmax and 171% and 121% for AUC in CYP2D6 EMs with mild and moderate hepatic impairment, respectively. (See Table 8)

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

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					Steady-state pharmacokinetics of eliglustat in CYP2D6 IMs and PMs with mild and moderate hepatic impairment is unknown. The effect of severe hepatic impairment in subjects with any CYP2D6 phenotype is unknown [see Use in Specific Populations (8.7)]. Drug Interaction Studies Effect of other drugs on CERDELGA Table 9 describes the effect of drug interactions on the pharmacokinetics of eliglustat [see Drug Interactions (7.1)]. (See Table 9) No clinically significant pharmacokinetic changes were observed for eliglustat when coadministered with intravenous rifampin (an OATP inhibitor), or gastric pH modifying drugs (e.g., aluminum hydroxide, magnesium hydroxide, calcium carbonate, pantoprazole). In vitro, eliglustat is a substrate of P-glycoprotein (P-gp). The effect of P-gp inhibitors on eliglustat pharmacokinetics is unknown. Effect of CERDELGA on other drugs CYP2D6 substrates Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage), metoprolol (a CYP2D6 substrate) mean Cmax and AUC increased by 1.7-fold and 2.3- fold in CYP2D6 EMs, respectively, and by 1.2-fold and 1.6-fold in IMs, respectively [see Drug Interactions (7.2)]. P-gp substrates Following multiple doses of CERDELGA 127 mg twice daily (1.5 times the recommended dosage) in CYP2D6 EMs and IMs, or 84 mg twice daily in PMs, digoxin (a P-gp substrate) mean Cmax increased by 1.7-fold and AUC increased by 1.5-fold [see Drug Interactions (7.2)]. **14 CLINICAL STUDIES** (…) The CERDELGA treatment group was comprised of IM (5%), EM (90%) and URM (5%) patients. (…)
125460, 02/14/2014	Elosulfase	Inborn Errors of Metabolism	GALNS	Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** Vimizim (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). **5 WARNINGS AND PRECAUTIONS** **5.2 Risk of Acute Respiratory Complications** Patients with acute febrile or respiratory illness at the time of Vimizim infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of Vimizim and consider delaying the Vimizim infusion. Sleep apnea is common in MPS IVA patients. Evaluation of airway patency should be considered prior to initiation of treatment with Vimizim. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an acute reaction, or extreme drowsiness/sleep induced by antihistamine use. **5.3 Spinal or Cervical Cord Compression** Spinal or cervical cord compression (SCC) is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease. In clinical trials, SCC was observed both in patients receiving Vimizim and patients receiving placebo. Patients with MPS IVA should be monitored for signs and symptoms of SCC (including back pain, paralysis of limbs below the level of compression, urinary and fecal incontinence) and given appropriate clinical care. **8 USE IN SPECIFIC POPULATIONS** *Clinical Considerations* *Disease-associated maternal and embryo/fetal risk* Pregnancy can adversely affect the health of females affected with MPS IVA and lead to adverse pregnancy outcomes for both mother and fetus. **8.3 Nursing Mothers** It is not known if Vimizim is present in human milk. Elosulfase alfa is present in milk from treated rats [see Use in Specific Populations (8.1)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Vimizim and any potential adverse effects on the breastfed child from the drug or from MPS IVA. Exercise caution when administering Vimizim to a nursing mother. There is a Morquio A Registry that also collects data on breastfeeding women with MPS IVA who are treated with Vimizim. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** The pharmacokinetics of elosulfase alfa were evaluated in 23 patients with MPS IVA who received intravenous infusions of Vimizim 2 mg/kg once weekly, over approximately 4 hours, for 22 weeks. (…) **14 CLINICAL STUDIES** The safety and efficacy of Vimizim were assessed in a 24-week, randomized, double-blind, placebo-controlled clinical trial of 176 patients with MPS IVA. (…)
022291, 11/16/2018	Eltrombopag (1)	Hematology	F5 (Factor V Leiden)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.3 Thrombotic/Thromboembolic Complications** Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). (…)
022291, 11/16/2018	Eltrombopag (2)	Hematology	SERPINC1 (Antithrombin III)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.3 Thrombotic/Thromboembolic Complications**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). (…)
022291, 11/16/2018	**Eltrombopag (3)**	Hematology	Chromosome 7del	Adverse Reactions	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Cytogenetic Abnormalities* In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M6 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality: 7 patients had the loss of chromosome 7, 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA. (…) (…) In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported on therapy, including 5 patients who had complex changes in chromosome 7.
022291, 11/16/2018	**Eltrombopag (4)**	Hematology	Chromosome 13del	Adverse Reactions	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Cytogenetic Abnormalities* In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M6 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality: 7 patients had the loss of chromosome 7, 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA. (…)
761107, 11/20/2018	**Emapalumab-lzsg**	Hematology	PRF1, RAB27A, SH2D1A, STXBP2, STX11, UNC13D, XIAP (Hemophagocytic Lymphohistiocytosis)	Clinical Studies	**14 CLINICAL STUDIES** (…) A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FHL3-UNC13D (MUNC 13-4) (26%), FHL2-PRF1 (19%), and Griscelli Syndrome type 2 (19%). The HLH mutations in the population enrolled are described in Table 3. (See Table 3)
209606, 08/01/2017	**Enasidenib**	Oncology	IDH2	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Acute Myeloid Leukemia** IDHIFA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of AML with IDHIFA based on the presence of IDH2 mutations in the blood or bone marrow [see Indications and Usage (1.1) and Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The potential for QTc prolongation with enasidenib was evaluated in an open-label study in patients with advanced hematologic malignancies with an IDH2 mutation. Based on the QTc data for a single dose of 30 mg to 650 mg and multiple doses of 100 mg daily in the fasted state, no large mean changes in the QTc interval (>20 ms) were observed following treatment with enasidenib. **14 CLINICAL STUDIES** **14.1 Acute Myeloid Leukemia** The efficacy of IDHIFA was evaluated in an open-label, single-arm, multicenter, two-cohort clinical trial (Study AG221-C-001, NCT01915498) of 199 adult patients with relapsed or refractory AML and an IDH2 mutation, who were assigned to receive 100 mg daily dose. Cohort 1 included 101 patients and Cohort 2 included 98 patients. IDH2 mutations were identified by a local diagnostic test and retrospectively confirmed by the Abbott RealTime™ IDH2 assay, or prospectively identified by the Abbott RealTime™ IDH2 assay, which is the FDA-approved test for selection of patients with AML for treatment with IDHIFA. (See Table 4) (…) (…) Efficacy was established on the basis of the rate of complete response (CR)/complete response with partial hematologic recovery (CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 5 and were similar in both cohorts. The median follow-up was 6.6 months (range, 0.4 to 27.7 months). Similar CR/CRh rates were observed in patients with either R140 or R172 mutation. (See Table 5) (…)

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
210496, 05/24/2019	**Encorafenib**	Oncology	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** BRAFTOVI™ is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test [see Dosage and Administration (2.1)]. Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI [see Warnings and Precautions (5.2), Clinical Studies (14)]. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics. **5 WARNINGS AND PRECAUTIONS** **5.2 Tumor Promotion in BRAF Wild-Type Tumors** In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation prior to initiating BRAFTOVI [see Indications and Usage (1), Dosage and Administration (2.1)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The safety of BRAFTOVI in combination with binimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS). (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib were observed in elderly patients as compared to younger patients [see Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg. After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg. Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%. **14 CLINICAL STUDIES** BRAFTOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. (…) (…) Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%). (…)
017087, 01/21/2010	**Enflurane**	Anesthesiology	Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)	Contraindications	**CONTRAINDICATIONS** (…) Known or suspected genetic susceptibility to malignant hyperthermia.
212018, 04/12/2019	**Erdafitinib (1)**	Oncology	FGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies, Patient Counseling Information	**1 INDICATIONS AND USAGE** BALVERSATM is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), that has: • susceptible FGFR3 or FGFR2 genetic alterations, and • progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA [see Dosage and Administration (2.1) and Clinical Studies (14)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of locally advanced or metastatic urothelial carcinoma with BALVERSA based on the presence of susceptible FGFR genetic alterations in tumor specimens as detected by an FDA-approved companion diagnostic [see Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of FGFR genetic alterations in urothelial cancer is available at: http://www.fda.gov/CcompanionDiagnostics. **6 ADVERSE REACTIONS**

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					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 safety of BALVERSA was evaluated in the BLC2001 study that included 87 patients with locally advanced or metastatic urothelial carcinoma which had susceptible FGFR3 or FGFR2 genetic alterations, and which progressed during or following at least one line of prior chemotherapy including within 12 months of neoadjuvant or adjuvant chemotherapy [see Clinical Studies (14.1)]. Patients were treated with BALVERSA at 8 mg orally once daily; with a dose increase to 9 mg in patients with phosphate levels <5.5 mg/dL on Day 14 of Cycle 1. Median duration of treatment was 5.3 months (range: 0 to 17 months). (…) **14 CLINICAL STUDIES** **14.1 Urothelial Carcinoma with Susceptible FGFR Genetic Alterations** Study BLC2001 (NCT02365597) was a multicenter, open-label, single-arm study to evaluate the efficacy and safety of BALVERSA in patients with locally advanced or metastatic urothelial carcinoma (mUC). Fibroblast growth factor receptor (FGFR) mutation status for screening and enrollment of patients was determined by a clinical trial assay (CTA). The efficacy population consists of a cohort of eighty-seven patients who were enrolled in this study with disease that had progressed on or after at least one prior chemotherapy and that had at least 1 of the following genetic alterations: FGFR3 gene mutations (R248C, S249C, G370C, Y373C) or FGFR gene fusions (FGFR3-TACC3, FGFR3 BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7), as determined by the CTA performed at a central laboratory. Tumor samples from 69 patients were tested retrospectively by the QIAGEN therascreen® FGFR RGQ RT-PCR Kit, which is the FDA-approved test for selection of patients with mUC for BALVERSA. (See Table 8) (…) **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Patient Information). FGFR genetic alterations: Advise patients that evidence of a susceptible FGFR3 or FGFR2 mutation or gene fusion within the tumor specimen is necessary to identify patients for whom treatment is indicated [see Dosage and Administration (2.1)].
212018, 04/12/2019	**Erdafitinib (2)**	Oncology	CYP2C9	Use in Specific Populations, Clinical Pharmacology	**8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2C9 Poor Metabolizers** CYP2C9*3/*3 Genotype: Erdafitinib plasma concentrations were predicted to be higher in patients with the CYP2C9*3/*3 genotype. Monitor for increased adverse reactions in patients who are known or suspected to have CYP2C9*3/*3 genotype [see Pharmacogenomics (12.5)]. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** CYP2C9 activity is reduced in individuals with genetic variants, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Erdafitinib exposure was similar in subjects with CYP2C9*1/*2 and *1/*3 genotypes relative to subjects with CYP2C9*1/*1 genotype (wild type). No data are available in subjects characterized by other genotypes (e.g., *2/*2, *2/*3, *3/*3). Simulation suggested no clinically meaningful differences in erdafitinib exposure in subjects with CYP2C9*2/*2 and *2/*3 genotypes. The exposure of erdafitinib is predicted to be 50% higher in subjects with the CYP2C9*3/*3 genotype, estimated to be present in 0.4% to 3% of the population among various ethnic groups.
201532, 10/19/2016	**Eribulin (1)**	Oncology	ERBB2 (HER2)	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Metastatic Breast Cancer** (…) Randomization was stratified by geographic region, HER2/neu status, and prior capecitabine exposure. HALAVEN was administered at a dose of 1.4 mg/m2 on Days 1 and 8 of a 21-day cycle. HALAVEN-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), and 3% hormonal therapy. The main efficacy outcome was overall survival. (…) **(…)** Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER , PR- , HER2/neu - : 19%), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (…)
201532, 10/19/2016	**Eribulin (2)**	Oncology	ESR, PGR (Hormone Receptor	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Metastatic Breast Cancer** **(…)** Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/neu receptor status (positive: 16%, negative: 74%), triple negative status (ER , PR- , HER2/neu - : 19%), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the HALAVEN and control arms. Patients received a median of four prior chemotherapy regimens in both arms. (See Table 5) (…)
021743, 10/18/2016	**Erlotinib**	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Non-Small Cell Lung Cancer (NSCLC)** TARCEVA® is indicated for: • The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen [see Clinical Studies (14.1, 14.3)]. Limitations of use: • Safety and efficacy of TARCEVA have not been established in patients with NSCLC whose tumors have other EGFR mutations [see Clinical Studies (14.1, 14.2)].

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

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					2 DOSAGE AND ADMINISTRATION **2.1 Selection of Patients with Metastatic NSCLC** Select patients for the treatment of metastatic NSCLC with TARCEVA based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor or plasma specimens [See Clinical Studies (14.1, 14.2)]. If these mutations are not detected in a plasma specimen, test tumor tissue if available. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** *Non-Small Cell Lung Cancer* *First-Line Treatment of Patients with EGFR Mutations* The most frequent (≥ 30%) adverse reactions in TARCEVA-treated patients were diarrhea, asthenia, rash, cough, dyspnea, and decreased appetite. In TARCEVA-treated patients the median time to onset of rash was 15 days and the median time to onset of diarrhea was 32 days. (…) **14 CLINICAL STUDIES** **14.1 Non-Small Cell Lung Cancer (NSCLC) – First-Line Treatment of Patients with EGFR Mutations** *Study 1* The safety and efficacy of TARCEVA as monotherapy for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or exon 21 (L858R) substitution mutations was demonstrated in Study 1, a randomized, open label, clinical trial conducted in Europe. One hundred seventy-four (174) White patients were randomized 1:1 to receive erlotinib 150 mg once daily until disease progression (n = 86) or four cycles of a standard platinum-based doublet chemotherapy (n = 88); standard chemotherapy regimens were cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. Randomization was stratified by EGFR mutation (exon 19 deletion or exon 21 (L858R) substitution) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1 vs. 2). EGFR mutation status for screening and enrollment of patients was determined by a clinical trials assay (CTA). Tumor samples from 134 patients (69 patients from the erlotinib arm and 65 patients from the chemotherapy arm) were tested retrospectively by the FDA-approved companion diagnostic, cobas® EGFR Mutation Test. (…) (…) The disease characteristics were 93% Stage IV and 7% Stage IIIb with pleural effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition), 93% adenocarcinoma, 66% exon 19 mutation deletions and 34% exon 21 (L858R) point mutation by CTA. (…) (…) In exploratory subgroup analyses based on EGFR mutation subtype, the hazard ratio (HR) for PFS was 0.27 (95% CI 0.17 to 0.43) in patients with exon 19 deletions and 0.52 (95% CI 0.29 to 0.95) in patients with exon 21 (L858R) substitution. The HR for OS was 0.94 (95% CI 0.57 to 1.54) in the exon 19 deletion subgroup and 0.99 (95% CI 0.56 to 1.76) in the exon 21 (L858R) substitution subgroup. **14.2 NSCLC - Lack of Efficacy of TARCEVA in Maintenance Treatment of Patients without EGFR Mutations** Lack of efficacy of TARCEVA for the maintenance treatment of patients with NSCLC without EGFR activating mutations was demonstrated in Study 2. Study 2 was a multicenter, placebo-controlled, randomized trial of 643 patients with advanced NSCLC without an EGFR exon 19 deletion or exon 21 L858R mutation who had not experienced disease progression after four cycles of platinum-based chemotherapy. (…) **14.3 NSCLC – Maintenance Treatment or Second/Third Line Treatment** Two randomized, double-blind, placebo-controlled trials, Studies 3 and 4, examined the efficacy and safety of TARCEVA administered to patients with metastatic NSCLC as maintenance therapy after initial treatment with chemotherapy (Study 3) or with disease progression following initial treatment with chemotherapy (Study 4). Determination of EGFR mutation status was not required for enrollment. (…) (…) Disease characteristics were as follows: Stage IV (75%), Stage IIIb with effusion (25%) as classified by AJCC (6th edition) with histologic subtypes of adenocarcinoma including bronchioalveolar (45%), squamous (40%) and large cell (5%); and EGFR IHC positive (70%), negative (14%), indeterminate (4%), and missing (12%). (…)
062759	**Erythromycin and Sulfisoxazole**	Infectious Diseases	G6PD	Precautions	Labeling not electronically available on Drugs@FDA
021323, 01/11/2019	**Escitalopram (1)**	Psychiatry	CYP2D6	Drug Interactions	**7 DRUG INTERACTIONS** **7.19 Drugs Metabolized by Cytochrome P4502D6** In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. (…)
021323, 01/11/2019	**Escitalopram (2)**	Psychiatry	CYP2C19	Adverse Reactions	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *ECG Changes* (…) Based on the established exposure-response relationship, the predicted QTcF change from placebo arm (95% confidence interval) under the Cmax for the dose of 20 mg is 6.6 (7.9) msec. Escitalopram 30 mg given once daily resulted in mean Cmax of 1.7-fold higher than the mean Cmax for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.
022101, 06/07/2018	**Esomeprazole**	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** **7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways**

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Last Updated: 06/2019

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					(…) Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers (Cmax and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (Cmax and AUC decreased by 49.6 % and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with NEXIUM. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* (…) CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.
206488, 10/11/2018	Eteplirsen	Neurology	DMD	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. 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. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian. (…) **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** 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, including pediatric patients [see Clinical Studies (14)]. (…) **14 CLINICAL STUDIES** EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. (…)
022334, 04/10/2018	**Everolimus (1)**	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clincal Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer** AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2 negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. **2 DOSAGE AND ADMINISTRATION** **2.2 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer** The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity. **5 WARNINGS AND PRECAUTIONS** **5.7 Geriatric Patients** In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [see Dosage and Administration (2.2), Use in Specific Populations (8.5)]. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Study Experience** Hormone Receptor-Positive, HER2 Negative Breast Cancer The safety of AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily) (n = 485) vs. placebo in combination with exemestane (n = 239) was evaluated in a randomized, controlled trial (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (28 to 93 years), and 75% were White. The median follow-up was approximately 13 months. (…) Topical Prophylaxis for Stomatitis In a single arm study (SWISH; N = 92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily), patients started dexamethasone 0.5 mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with AFINITOR and exemestane. (…) **8 USE IN SPECIFIC POPULATIONS**

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

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					Other Indications The safety and effectiveness of AFINITOR/AFINITOR DISPERZ in pediatric patients have not been established in: • Hormone receptor-positive, HER2-negative breast cancer (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** (…) The coadministration of AFINITOR with exemestane increased exemestane Cmin by 45% and C2h by 64%; however, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination. (…) **14 CLINICAL STUDIES** **14.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer** A randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. (See Table 20 and Figure 1) (…)
022334, 04/10/2018	**Everolimus (2)**	Oncology	ESR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer** AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. **2 DOSAGE AND ADMINISTRATION** 2.2 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity. **5 WARNINGS AND PRECAUTIONS** 5.8 Geriatric Patients In the randomized hormone receptor-positive, HER2-negative breast cancer study (BOLERO-2), the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [see Dosage and Administration (2.9), Use in Specific Populations (8.5)]. **6 ADVERSE REACTIONS** **6.1 Clinical Study Experience** Hormone Receptor-Positive, HER2 Negative Breast Cancer The safety of AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily) (n = 485) vs. placebo in combination with exemestane (n = 239) was evaluated in a randomized, controlled trial (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (28 to 93 years), and 75% were White. The median follow-up was approximately 13 months. (See Tables 6 and 7) (…) Topical Prophylaxis for Stomatitis In a single arm study (SWISH; N = 92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily), patients started dexamethasone 0.5 mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with AFINITOR and exemestane. (…) **8 USE IN SPECIFIC POPULATIONS** Other Indications The safety and effectiveness of AFINITOR/AFINITOR DISPERZ in pediatric patients have not been established in: • Hormone receptor-positive, HER2-negative breast cancer (…) **8.5 Geriatric Use** In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness were observed between elderly and younger patients. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** (…) The coadministration of AFINITOR with exemestane increased exemestane Cmin by 45% and C2h by 64%; however, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination. (…) **14 CLINICAL STUDIES** **14.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer**

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Last Updated: 06/2019

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020753, 05/18/2018	Exemestane	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Adjuvant Treatment of Postmenopausal Women** AROMASIN is indicated for adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy [see Clinical Studies (14.1)]. (…) **2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dose** The recommended dose of AROMASIN in early and advanced breast cancer is one 25 mg tablet once daily after a meal. • adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy. (…) **14 CLINICAL STUDIES** **14.1 Adjuvant Treatment in Early Breast Cancer** The Intergroup Exemestane Study 031 (IES) was a randomized, double-blind, multicenter, multinational study comparing exemestane (25 mg/day) vs. tamoxifen (20 or 30 mg/day) in postmenopausal women with early breast cancer. (See Table 5) (…) (…) In the hormone receptor-positive subpopulation representing about 85% of the trial patients, disease-free survival was also statistically significantly improved (HR = 0.65, 95% CI: 0.53, 0.79, P = 0.00001) in the AROMASIN arm compared to the tamoxifen arm. Consistent results were observed in the subgroups of patients with node negative or positive disease, and patients who had or had not received prior chemotherapy. (See Table 9) (…)
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. Coadministration of the potent CYP3A4 inhibitor ketoconazole with fesoterodine led to approximately a doubling of the maximum concentration (Cmax) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of fesoterodine. Compared with CYP2D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole [see Clinical Pharmacology (12.3), Warnings and Precautions (5.8), and Dosage and Administration (2)]. (…) **7.4 CYP2D6 Inhibitors** The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors. **12 CLINICAL PHARMACOLOGY** **12.2 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 coadministration 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 were 4.5- and 5.7-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 3.4- and 4.2 fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. There is no clinically relevant effect of moderate CYP3A4 inhibitors on the pharmacokinetics of fesoterodine. (…) *CYP2D6 Inhibitors:* The interaction with CYP2D6 inhibitors was not studied. In poor metabolizers for CYP2D6, 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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Last Updated: 06/2019

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022526, 08/18/2015	Flibanserin (1)	Gynecology	CYP2C9	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes. *CYP2C9 Poor Metabolizers* A study comparing flibanserin exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C9 inhibitor. In 8 women who were poor metabolizers of CYP2C9, Cmax and AUC0-inf of flibanserin 100 mg once daily decreased 23% and 18%, compared to exposures among 8 extensive metabolizers of CYP2C9.
022526, 08/18/2015	Flibanserin (2)	Gynecology	CYP2C19	Adverse Reactions, Use in Specific Populations, Clinical Pharmacology	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Syncope in Poor CYP2C19 Metabolizers* In a pharmacogenomic study of 100 mg ADDYI in subjects who were poor or extensive CYP2C19 metabolizers, syncope occurred in 1/9 (11%) subjects who were CYP2C19 poor metabolizers (this subject had a 3.2 fold higher flibanserin exposure compared to CYP2C19 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C19 extensive metabolizers [see Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)]. **8 USE IN SPECIFIC POPULATIONS** **8.7 CYP2C19 Poor Metabolizers** CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer [see Adverse Reactions (6.1) and Clinical Pharmacology (12.5)]. Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes. *CYP2C19 Poor Metabolizers* A study comparing flibanserin exposure in CYP2C19 poor metabolizers to CYP2C19 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C19 inhibitor. In 9 women who were poor metabolizers of CYP2C19, Cmax and AUC0-inf of flibanserin 100 mg once daily increased 1.5-fold (1.1-2.1) and 1.3-fold (0.9-2.1), compared to exposures among 8 extensive metabolizers of CYP2C19. Flibanserin half-life was increased from 11.1 hours in the extensive metabolizers of CYP2C19 to 13.5 hours in the poor metabolizers of CYP2C19 [see Adverse Reactions (6.1) and Use in Specific Populations (8.7)]. The frequencies of poor metabolizers of CYP2C19 are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.
022526, 08/18/2015	Flibanserin (3)	Gynecology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes. *CYP2D6 Poor Metabolizers* A study comparing flibanserin exposure in CYP2D6 poor metabolizers to CYP2D6 extensive metabolizers was conducted in addition to a drug interaction study with paroxetine, a strong CYP2D6 inhibitor. In 12 poor metabolizers of CYP2D6, steady state Cmax and AUC of flibanserin 50 mg twice daily was decreased by 4% and increased by 18%, respectively, compared to exposures among 19 extensive metabolizers, intermediate metabolizers and ultra rapid metabolizers of CYP2D6.
020985, 12/16/2003	Fluorouracil (1)	Dermatology	DPYD	Contraindications, Warnings	**CONTRAINDICATIONS** (…) Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. (…) **WARNINGS** The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive. Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop. Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parental administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil. Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

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

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012209, 07/29/2016	Fluorouracil (2)	Oncology	DPYD	Warnings and Precautions, Patient Counseling Information	**5 WARNINGS AND PRECAUTIONS** **5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase (DPD) Activity** Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test. **17 PATIENT COUNSELING INFORMATION** Advise: • Patients to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity, they are at an increased risk of severe and life-threatening mucositis, diarrhea, neutropenia and neurotoxicity [see Warnings and Precautions (5.1)]. (…)
020101, 01/30/2009	Fluoxetine	Psychiatry	CYP2D6	Precautions, Clinical Pharmacology	**PRECAUTIONS** *Drug Interactions* 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 potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (see CONTRAINDICATIONS and WARNINGS). **CLINICAL PHARMACOLOGY** *Clinical issues related to metabolism/elimination* The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use. Variability in metabolism- A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. (…)
018766, 05/09/2016	Flurbiprofen	Rheumatology	CYP2C9	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Poor Metabolizers of CYP2C9 Substrates* In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.
018554, 07/23/2001	Flutamide	Oncology	G6PD	Warnings	**WARNINGS** **Aniline Toxicity:** One metabolite of flutamide is 4-nitro-3-fluoromethylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (e.g., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease and smokers), monitoring of methemoglobin levels should be considered.
022007, 05/29/2019	Formoterol (1)	Pulmonary	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.
022007, 05/29/2019	Formoterol (2)	Pulmonary	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* (…) Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

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Last Updated: 06/2019

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020450, 10/31/2017	**Fosphenytoin**	Neurology	HLA-B	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.4 Serious Dermatologic Reactions** Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and StevensJohnson syndrome (SJS), have been reported with phenytoin (the active metabolite of CEREBYX) treatment. The onset of symptoms is usually within 28 days,but can occur later. CEREBYX should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.5)]. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding CEREBYX as an alternative for carbamazepine patients positive for HLA-B*1502. The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.
022033, 01/04/2017	**Fluvoxamine**	Psychiatry	CYP2D6	Drug Interactions	**7 DRUG INTERACTIONS** **7.1 Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes** (…) Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as “poor metabolizers” (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an in vivo study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 “extensive metabolizers” (EM): mean Cmax, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patient known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine). (…)
021344, 05/20/2019	**Fulvestrant (1)**	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** Monotherapy FASLODEX is indicated for the treatment of: • Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or • HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. Combination Therapy FASLODEX is indicated for the treatment of: • HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy. • HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Combination Therapy Combination Therapy with Palbociclib (PALOMA-3) The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months. (…) Combination Therapy with Abemaciclib (MONARCH 2) The safety of FASLODEX (500 mg) plus abemaciclib (150 mg twice daily) versus FASLODEX plus placebo was evaluated in MONARCH 2. The data described below reflect exposure to FASLODEX in 664 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (…) Combination Therapy with Ribociclib (MONALEESA-3) The safety of FASLODEX 500 mg plus ribociclib 600 mg versus FASLODEX plus placebo was evaluated in MONALEESA-3. The data described below reflect exposure to FASLODEX plus ribociclib in 483 out of 724 postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy who received at least one dose of FASLODEX plus ribociclib or placebo in MONALEESA-3. Median duration of treatment was 15.8 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (…) **14 CLINICAL STUDIES** Comparison of FASLODEX 500 mg and Anastrozole 1 mg (FALCON) A randomized, double-blind, double-dummy, multi-center study (FALCON, NCT01602380) of FASLODEX 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-positive, HER2-negative locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy. (…) Combination Therapy

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Last Updated: 06/2019

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					Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy FASLODEX 500 mg in Combination with Palbociclib 125 mg (PALOMA-3) PALOMA-3 (NCT-1942135) was an international, randomized, double-blind, parallel group, multi-center study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with HRpositive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…) FASLODEX 500 mg in Combination with Abemaciclib 150 mg (MONARCH 2) MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multi-center study conducted in women with HR-positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy treated with FASLODEX plus abemaciclib versus FASLODEX plus placebo. (…) Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy FASLODEX 500 mg in Combination with Ribociclib 600 mg (MONALEESA-3) MONALEESA-3 (NCT 02422615) was a randomized double-blind, placebo-controlled study of FASLODEX plus ribociclib versus FASLODEX plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)
021344, 05/20/2019	**Fulvestrant (2)**	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** Monotherapy FASLODEX is indicated for the treatment of: • Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or • HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. Combination Therapy FASLODEX is indicated for the treatment of: • HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy. • HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Comparison of FASLODEX 500 mg and Anastrozole 1 mg (FALCON) The safety of FASLODEX 500 mg versus anastrozole 1 mg was evaluated in FALCON. The data described below reflect exposure to FASLODEX in 228 out of 460 patients with HR-positive advanced breast cancer in postmenopausal women not previously treated with endocrine therapy who received at least one (1) dose of treatment in FALCON. (…) Combination Therapy Combination Therapy with Palbociclib (PALOMA-3) The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months. (…) Combination Therapy with Abemaciclib (MONARCH 2) The safety of FASLODEX (500 mg) plus abemaciclib (150 mg twice daily) versus FASLODEX plus placebo was evaluated in MONARCH 2. The data described below reflect exposure to FASLODEX in 664 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2. (…) Combination Therapy with Ribociclib (MONALEESA-3) The safety of FASLODEX 500 mg plus ribociclib 600 mg versus FASLODEX plus placebo was evaluated in MONALEESA-3. The data described below reflect exposure to FASLODEX plus ribociclib in 483 out of 724 postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy who received at least one dose of FASLODEX plus ribociclib or placebo in MONALEESA-3. Median duration of treatment was 15.8 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo. (…) **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation. **14 CLINICAL STUDIES** Combination Therapy

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021169, 02/14/2017	Galantamine	Neurology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and Elimination* Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly. O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In studies of oral 3 H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average. (…) (…) RAZADYNE® ER 24 mg extended-release capsules administered once daily under fasting conditions are bioequivalent to RAZADYNE® tablets 12 mg twice daily with respect to AUC24h and Cmin. The Cmax and Tmax of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with Cmax about 25% lower and median Tmax occurring about 4.5–5.0 hours after dosing. Dose-proportionality is observed for RAZADYNE® ER extended-release capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER extended-release capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. (…) *CYP2D6 Poor Metabolizers* Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% AUC_{∞} increase of unchanged galantamine compared to extensive metabolizers. A total of 356 patients with Alzheimer's disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.
206995, 08/22/2018	Gefitinib (1)	Oncology	EGFR	Indications and Usage, Dosage and Administration, Clinical Studies	**1 INDICATIONS AND USAGE** IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by 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 demonstrated in a multicenter, single-arm, open-label clinical study (Study 1). A total of 106 treatment-naive patients with metastatic EGFR mutation positive NSCLC received IRESSA at a dose of 250 mg once daily until disease progression or intolerable toxicity. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by both a Blinded Independent Central Review (BICR) and investigators. Duration of response (DOR) was an additional outcome measure. Eligible patients were required to have a deletion in EGFR exon 19 or L858R, L861Q, or G719X

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					substitution mutation and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. Tumor samples from 87 patients were tested retrospectively using the therascreen® EGFR RGQ PCR Kit. The study population characteristics were: median age 65 years, age 75 years or older (25%), age less than 65 years (49%), white (100%), female (71%), never smokers (64%), WHO PS 0 (45%), WHO PS 1 (48%), WHO PS 2 (7%), and adenocarcinoma histology (97%). Sixty patients had exon 19 deletions (65%), 29 patients had L858R substitution (31%), while two patients each had tumors harboring L861Q or G719X substitution mutation. The median duration of treatment was 8.0 months. (See Table 3) The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation with duration of response of at least 2.8 months and 5.6 months, respectively. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response with duration of response of at least 2.8 months. *Study 2* The results of Study 1 were supported by an exploratory analysis of a subset of a randomized, multicenter, open-label trial (Study 2) conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients were randomized (1:1) to receive IRESSA 250 mg orally once daily or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and objective response rate (ORR) as assessed by BICR. The subset population consisted of 186 of 1217 patients (15%) determined to be EGFR positive by the same clinical trial assay as used in Study 1 and had radiographic scans available for a retrospective assessment by BICR. In this subset, there were 88 IRESSA-treated patients and 98 carboplatin/paclitaxel-treated patients. (…)
206995, 08/22/2018	**Gefitinib (2)**	Oncology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** CYP2D6 Poor metabolizer: CYP2D6 metabolizes gefitinib to O-desmethyl gefitinib in vitro. In healthy CYP2D6 poor metabolizers, O-desmethyl gefitinib concentration was not measurable and the mean exposure to gefitinib was 2-fold higher as compared to the extensive metabolizers. This increase in exposure in CYP2D6 poor metabolizers may be clinically important because some adverse drug reactions are related to higher exposure of gefitinib. No dose adjustment is recommended in patients with a known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse reactions. The impact of CYP2D6 inhibiting drugs on gefitinib pharmacokinetics has not been evaluated. However, similar precautions should be used when administering CYP2D6 inhibitors with IRESSA because of the possibility of increased exposure in these patients. An exploratory exposure response analysis showed an increase in the incidence of interstitial lung disease (ILD) with a greater than 2 fold increase in the gefitinib exposure [see Warnings and Precautions (5.1)].
211349, 05/29/2019	**Gilteritinib**	Oncology	FLT3	Indications and Usage, Dosage and Administration, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Relapsed or Refractory Acute Myeloid Leukemia** XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at http://www.fda.gov/CompanionDiagnostics. **14 CLINICAL STUDIES** **14.1 Relapsed or Refractory Acute Myeloid Leukemia** The efficacy of XOSPATA was assessed in the ADMIRAL trial (NCT02421939), which included 138 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. (See Table 4) (…) (…) For patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only. (See Table 6) (…) (…) In the final analysis, the CR/CRh rate in the gilteritinib arm was 22.6% (55/243) and the DOR was 7.4 months (range, <0.1 + to 23.1+). For patients who achieved a CR/CRh, the median time to first response was 2 months (range, 0.9 to 9.6 months). The CR/CRh rate was 49 of 215 in patients with FLT3-ITD only, 3 of 7 in patients with FLT3-ITD/TKD and 3 of 21 in patients with FLT3-TKD only. (…)
020496, 12/21/2018	**Glimepiride**	Endocrinology	G6PD	Warnings and Precautions, Adverse Reactions	**5 WARNINGS AND PRECAUTIONS** **5.3 Hemolytic Anemia** Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving AMARYL who did not have known G6PD deficiency [see Adverse Reactions (6.2)]. **6 ADVERSE REACTIONS** **6.2 Postmarketing Experience** The following adverse reactions have been identified during post-approval use of AMARYL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. (…) • Hemolytic anemia in patients with and without G6PD deficiency [see Warnings and Precautions (5.3)] (…)
017783, 08/18/2016	**Glipizide**	Endocrinology	G6PD	Precautions	**PRECAUTIONS** *Hemolytic Anemia*

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					Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLUCOTROL belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.
020051, 08/22/2017	**Glyburide**	Endocrinology	G6PD	Precautions	**PRECAUTIONS** *Hemolytic Anemia* Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLYNASE PresTab belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.
019726, 02/12/2015	**Goserelin**	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.5 Advanced Breast Cancer** ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women. The estrogen and progesterone receptor values may help to predict whether ZOLADEX therapy is likely to be beneficial [see Dosage and Administration (2.6), Clinical Pharmacology (12.1), and Clinical Studies (14.5)]. **14 CLINICAL STUDIES** **14.5 Breast Cancer** The Southwest Oncology Group conducted a prospective, randomized clinical trial (SWOG-8692 [INT-0075]) in premenopausal women with advanced estrogen receptor positive or progesterone receptor positive breast cancer which compared ZOLADEX with oophorectomy. (…) (…) Findings were similar in uncontrolled clinical trials involving patients with hormone receptor positive and negative breast cancer. Premenopausal women with estrogen receptor (ER) status of positive, negative, or unknown participated in the uncontrolled (Phase II and Trial 2302) clinical trials. Objective tumor responses were seen regardless of ER status, as shown in the following table. (See Table 8)
020727, 03/12/2019	**Hydralazine**	Cardiology	Nonspecific (NAT)	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Absorption* (…) Hydralazine hydrochloride: About 2/3 of a 50-mg dose of 14C-hydralazine hydrochloride given in gelatin capsules was absorbed in hypertensive subjects. In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to 26%, with the higher percentages in slow acetylators. Administration of doses escalating from 75 mg to 1000 mg three times daily to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-linear kinetics of hydralazine, probably reflecting saturable first pass metabolism. (…) *Metabolism* Hydralazine is metabolized by acetylation, ring oxidation and conjugation with endogenous compounds including pyruvic acid. Acetylation occurs predominantly during the first-pass after oral administration which explains the dependence of the absolute bioavailability on the acetylator phenotype. About 50% of patients are fast acetylators and have lower exposure. (…)
009768, 01/27/2017	**Hydroxychloroquine**	Infectious Diseases	G6PD	Precautions, Adverse Reactions	**PRECAUTIONS** (…) PLAQUENIL should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…) **ADVERSE REACTIONS** **Blood and lymphatic system disorders**: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. (…)
205552, 01/25/2019	**Ibrutinib (1)**	Oncology	Chromosome 17p	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion** IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [see Clinical Studies (14.2)]. **14 CLINICAL STUDIES** **14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma** *RESONATE* (…) Thirty-two percent of patients had 17p deletion. (…) *CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE* RESONATE included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for del 17p CLL/SLL are shown in Table 19. (See Table 19) 63-Month Follow-Up With an overall follow-up of 63 months, the median investigator-assessed PFS in patients with del 17p per IWCLL criteria was 40.6 months [95% CI (25.4, 44.6)] in the IMBRUVICA arm and 6.2 months [95% CI (4.6, 8.1)] in the ofatumumab arm, respectively. Overall response rate as assessed by investigators in patients with del 17p was 88.9% in the IMBRUVICA arm versus 18.8% in the ofatumumab arm. *iLLUMINATE* The iLLUMINATE study (a multi-center study of ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab) (NCT02264574) was conducted in patients with treatment naïve CLL or SLL. Patients were 65 years of age or older or < 65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance < 70 mL/min, or presence of del 17p/TP53 mutation. (…)

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					The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy included: lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%). (…) In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].
205552, 01/25/2019	**Ibrutinib (2)**	Oncology	Chromosome 11q	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma** *RESONATE-2* (…) 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%). (…) *HELIOS* (…) 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. (…) The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy included: lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%). (…) In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].
022192, 02/23/2017	**Iloperidone**	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.2 Dosage in Special Populations** *Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6* FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6 [see Clinical Pharmacology (12.3)]. **5 WARNINGS AND PRECAUTIONS** **5.3 QT Prolongation** (…) Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism [see Drug Interactions (7.1)], and in patients with reduced activity of CYP2D6 [see Clinical Pharmacology (12.3)]. (…) **7 DRUG INTERACTIONS** **7.1 Potential for Other Drugs to Affect FANAPT** *Fluoxetine:* Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2- to 3-fold, and decreased the AUC of its metabolite P95 by one-half. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3 -4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4. *Metabolism and Elimination* Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. Approximately 7% - 10% of Caucasians and 3% - 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers. Coadministration of FANAPT with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3- fold increase in iloperidone plasma exposure, and therefore one-half of the FANAPT dose should be administered. Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs. The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.
021588, 08/21/2018	**Imatinib (1)**	Oncology	KIT	Indications and Usage, Dosage and	**1 INDICATIONS AND USAGE** **1.6 Aggressive Systemic Mastocytosis (ASM)** Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test [see Dosage and Administration (2.7)] or with c-Kit mutational status unknown.

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				Administration, Clinical Studies	**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. **2 DOSAGE AND ADMINISTRATION** **2.7 Adult Patients with ASM** Determine D816V c-Kit mutation status prior to initiating treatment. Information on FDA-approved test for the detection of D816V c-Kit mutation is available at http://www.fda.gov/companiondiagnostics. The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If cKit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. **14 CLINICAL STUDIES** **14.5 Myelodysplastic/Myeloproliferative Diseases** An open-label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) **14.6 Aggressive Systemic Mastocytosis** One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) (…) 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. (…) (…) Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec. **14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia** One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) **14.8 Dermatofibrosarcoma Protuberans** (…) 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. (…) **14.9 Gastrointestinal Stromal Tumors** (…) One open-label, multinational Phase 2 study was conducted in patients with Kit (CD117) positive unresectable or metastatic malignant GIST. (…) *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 immunochemistry 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 10/50 HPF, or tumors ruptured into the peritoneal cavity. (…)
021588, 08/21/2018	**Imatinib (2)**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**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** **2.2 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

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					months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response. **2.3 Pediatric Patients with Ph+ CML CP** The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m^2 /day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with Gleevec treatment in children under 1 year of age. **2.4 Adult Patients with Ph+ ALL** The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL. **2.5 Pediatric Patients with Ph+ ALL** The recommended dose of Gleevec to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m^2/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose. **2.14 Dose Adjustment for Hematologic Adverse Reactions** Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (…) **5 WARNINGS AND PRECAUTIONS** **5.1 Fluid Retention and Edema** (…) In a randomized trial in patients with newly diagnosed Ph+CML in chronic phase comparing Gleevec and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Gleevec and in 3.9% of patients receiving nilotinib 300 mg bid. (…) **5.3 Congestive Heart Failure and Left Ventricular Dysfunction** (…) In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. In another randomized trial with newly diagnosed Ph+ CML patients in chronic phase that compared Gleevec and nilotinib, cardiac failure was observed in 1.1% of 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. (Seee Table 3) (…) **6.2 Adverse Reactions in Pediatric Population** *In combination with multi-agent chemotherapy* (…) Patients with Ph+ ALL (n=92) were assigned to receive Gleevec and treated in 5 successive cohorts. Gleevec exposure was systematically increased in successive cohorts by earlier introduction and more prolonged duration. The safety of Gleevec given in combination with intensive chemotherapy was evaluated by comparing the incidence of grade 3 and 4 adverse events, neutropenia (less than 750/mcL) and thrombocytopenia (less than 75,000/mcL) in the 92 patients with Ph+ ALL compared to 65 patients with Ph- ALL enrolled on the trial who did not receive Gleevec. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Gleevec. The protocol included up to 18 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Gleevec and 647 without Gleevec. The adverse events that were reported with a 5% or greater incidence in patients with Ph+ ALL compared to Ph- ALL or with a 1% or greater incidence in cycles of therapy that included Gleevec are presented in Table 8. (See Table 8) (…) **6.4 Acute Lymphoblastic Leukemia** The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps and rash. Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb 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.

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

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					12 CLINICAL PHARMACOLOGY **12.3 Pharmacokinetics** *Pediatric Use* (…) Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, Ph+ ALL, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in pediatric patients receiving 260 mg/m2 once-daily (not exceeding 400 mg once-daily) or 340 mg/m2 once-daily (not exceeding 600 mg once-daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once-daily. **14 CLINICAL STUDIES** **14.1 Chronic Myeloid Leukemia** *Chronic Phase, Newly Diagnosed* An open-label, multicenter, international randomized Phase 3 study (Gleevec versus IFN+Ara-C) has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (See Table 18) (…) (…) An open-label, multicenter, randomized trial (Gleevec versus nilotinib) was conducted to determine the efficacy of Gleevec versus nilotinib in adult patients with cytogenetically confirmed, newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. (See Table 19) (…) (…) *Late Chronic Phase CML and Advanced Stage CML:* Three international, open-label, single-arm phase 2 studies were conducted to determine the safety and efficacy of Gleevec in patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were black. In clinical studies, 38%–40% of patients were ≥60 years of age and 10%–12% of patients were ≥70 years of age. (…) *Chronic Phase, Prior Interferon-Alpha Treatment:* Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). (…) **14.2 Pediatric CML** One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. (…) (…) In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m^2/day. **14.3 Acute Lymphoblastic Leukemia** A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease were studied, 43 of whom received the recommended Gleevec dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL received Gleevec 600 mg/day in a phase 1 study. Confirmed and unconfirmed hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 21. The median duration of hematologic response was 3.4 months and the median duration of MCyR was 2.3 months. (See Table 21) (…) **14.4 Pediatric ALL** Pediatric and young adult patients with very high risk ALL, defined as those with an expected 5-year event-free survival (EFS) less than 45%, were enrolled after induction therapy on a multicenter, non-randomized cooperative group pilot protocol. The safety and effectiveness of Gleevec (340 mg/m^2/day) in combination with intensive chemotherapy was evaluated in a subgroup of patients with Ph+ ALL. The protocol included intensive chemotherapy and hematopoietic stem cell transplant after 2 courses of chemotherapy for patients with an appropriate HLA-matched family donor. There were 92 eligible patients with Ph+ ALL enrolled. (…) (…) There were 50 patients with Ph+ ALL assigned to cohort 5 all of whom received Gleevec plus chemotherapy; 30 were treated exclusively with chemotherapy and Gleevec and 20 received chemotherapy plus Gleevec and then underwent hematopoietic stem cell transplant, followed by further Gleevec treatment. (…)
021588, 08/21/2018	Imatinib (3)	Oncology	PDGFRB	Indications and Usage, Dosage and Administration, Clinical Studies	**1 INDICATIONS AND USAGE** **1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)** Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test [see Dosage and Administration (2.6)]. **2 DOSAGE AND ADMINISTRATION** **2.6 Adult Patients with MDS/MPD** Determine PDGFRb gene rearrangements status prior to initiating treatment. Information on FDA-approved tests for the detection of PDGFRb rearrangements is available at http://www.fda.gov/companiondiagnostics. The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD. **14 CLINICAL STUDIES** **14.5 Myelodysplastic/Myeloproliferative Diseases** An open-label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) (…) Sixteen patients had a translocation, involving chromosome 5q33 or 4q12, resulting in a PDGFR gene rearrangement. All of these patients responded hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1 (7%) out

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Last Updated: 06/2019

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					of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8–26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in Table 22. Response durations of phase 2 study patients ranged from 141+ days to 457+ days. (See Table 22) **14.6 Aggressive Systemic Mastocytosis** One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) **14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia** One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) **14.8 Dermatofibrosarcoma Protuberans** Dermatofibrosarcoma Protuberans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22 that results in the fusion of the collagen type 1 alpha 1 gene and the PDGF B gene. An open-label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. (…) (…) Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. (See Table 25) (…) (…) For the 10 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.
021588, 08/21/2018	**Imatinib (4)**	Oncology	FIP1L1-PDGFRA	Indications and Usage, Dosage and Administration, Clinical Studies	**1 INDICATIONS AND USAGE** **1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)** Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown. **2.7 Adult Patients with ASM** Determine D816V c-Kit mutation status prior to initiating treatment. Information on FDA-approved test for the detection of D816V c-Kit mutation is available at http://www.fda.gov/companiondiagnostics. The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If cKit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. **2.8 Adult Patients with HES/CEL** The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. **2.14 Dose Adjustment for Hematologic Adverse Reactions** Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1. (See Table 1) (…) **14 CLINICAL STUDIES** **14.6 Aggressive Systemic Mastocytosis** (…) Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this 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) (…)
017090, 07/28/2014	**Imipramine**	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Drug Interactions* *Drugs Metabolized by P450 2D6* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). (…)
022383, 05/29/2019	**Indacaterol**	Pulmonary	UGT1A1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.4 Pharmacogenomics** The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as *28) and the (TA)6, (TA)6 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.

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Table of Pharmacogenomic Biomarkers in Drug Labeling

Last Updated: 06/2019

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211172, 10/05/2018	Inotersen	Neurology	TTR	Adverse Reactions, Clinical Pharmacology	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) Baseline disease characteristics were largely similar in TEGSEDI-treated patients and patients in the placebo control group. Sixty-seven percent of patients were in Stage 1 of the disease at baseline, and 33% in Stage 2. Fifty-two percent of patients had Val30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different other point mutations. (…) **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** The pharmacodynamic effects of TEGSEDI were evaluated in hATTR amyloidosis patients treated with 284 mg TEGSEDI via subcutaneous injection once weekly. With repeat dosing, the mean percent decreases from baseline in serum TTR from Week 13 to Week 65 of treatment ranged from 68% to 74% (median range: 75% to 79%). Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race. (…)
761040, 08/17/2017	Inotuzumab Ozogamicin	Oncology	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies	**14 CLINICAL STUDIES** **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. (…) (…) The median age was 47 years (range: 18-79 years), 276 patients (85%) had Philadelphia chromosome-negative ALL, 206 patients (63%) had a duration of first remission < 12 months, and 55 patients (17%) had undergone a HSCT prior to receiving BESPONSA or Investigator's choice of chemotherapy. (…)
125377, 05/08/2019	Ipilimumab (1)	Oncology	HLA-A	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Unresectable or Metastatic Melanoma** The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094653) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. (…)
125377, 05/08/2019	Ipilimumab (2)	Oncology	Microsatellite Instability, Mismatch Repair	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** **1.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer** YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.4)]. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma; and to YERVOY 1 mg/kg, administered in combination with nivolumab, in two trials: CHECKMATE214 (NCT02231749), a randomized trial in previously untreated patients with advanced renal cell carcinoma, and CHECKMATE-142 (NCT02060188), an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer. (…) **Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer** The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, nonrandomized, multiple parallel-cohort study. In CHECKMATE-142, 119 patients with previously treated MSI-H or dMMR mCRC received YERVOY, in combination with nivolumab, in a singlearm cohort. In another single-arm cohort under CHECKMATE-142, 74 patients with mCRC received nivolumab monotherapy. (See Tables 9 and 10) (…) **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma or for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY in this age group is supported by evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacokinetic data demonstrating that the exposure at doses of 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of advanced melanoma and MSI-H or dMMR metastatic colorectal cancer are sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients. (…) **14 CLINICAL STUDIES** **14.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer**

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Last Updated: 06/2019

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					CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallelcohort, open-label study conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG PS 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients enrolled in the YERVOY and nivolumab MSI-H mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks. Patients enrolled in the single-agent nivolumab MSI-H mCRC cohort received nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (See Table 14) (…)
020571, 02/22/2019	Irinotecan	Oncology	UGT1A1	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.3 Dosage in Patients with Reduced UGT1A1 Activity** When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele [see Dosage and Administration (2.1 and 2.2) and Warnings and Precautions (5.3)]. However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment (See Tables 1-4). **5 WARNINGS AND PRECAUTIONS** **5.3 Patients With Reduced UGT1A1 Activity** Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m2 once-every-3- weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype). In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4.5%, and in patients heterozygous for this allele the incidence was 5.3%. Grade 4 neutropenia was observed in 1.8% of patients homozygous for the wild-type allele. In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18.2%, and in patients heterozygous for this allele the incidence was 11.1%. Grade 4 neutropenia was observed in 6.8% of patients homozygous for the wildtype allele. When administered in combination with other agents or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment [see Dosage and Administration (2)]. *UGT1A1 Testing* A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4- mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In vitro studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m^2) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype) [see Warnings and Precautions (5.3) and Dosage and Administration (2.3)]. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro.
017624, 04/27/2017	Isoflurane	Anesthesiology	Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)	Contraindications	**CONTRAINDICATIONS** Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.
050705, 02/28/2019	Isoniazid, Pyrazinamide, and Rifampin	Infectious Diseases	Nonspecific (NAT)	Clinical Pharmacology	**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.
019790, 10/24/2014	Isosorbide Dinitrate	Cardiology	CYB5R	Overdosage	**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

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					mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide dinitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8-6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.
020215, 10/02/2014	**Isosorbide Mononitrate**	Cardiology	CYB5R	Overdosage	**OVERDOSAGE** *Methemoglobinemia* Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8-11.1 mg of isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial p02. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.
203188, 04/29/2019	**Ivacaftor**	Pulmonary	CFTR	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. **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 pooled data from three placebo-controlled clinical trials conducted in 353 patients 6 years of age and older with CF who had a G551D mutation in the CFTR gene (Trials 1 and 2) or were homozygous for the F508del mutation (Trial 3). In addition, the following clinical trials have also been conducted [see Clinical Pharmacology (12) and Clinical Studies (14)]: • An 8-week, crossover design trial (Trial 4) involving 39 patients between the ages of 6 and 57 years with a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. • A 24-week, placebo-controlled trial (Trial 5) involving 69 patients between the ages of 6 and 68 years with an R117H mutation in the CFTR gene. • A 24-week, open-label trial (Trial 6) in 34 patients 2 to less than 6 years of age. Patients eligible for Trial 6 were those with the G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. Of 34 patients enrolled, 32 had the G551D mutation and 2 had the S549N mutation. • An 8-week, crossover design trial (Trial 7) involving patients between the ages of 12 and 72 years who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO. • A cohort of 19 patients aged 12 months to less than 24 months, and a cohort of 11 patients aged 6 months to less than 12 months in a 24-week, open-label clinical trial in patients with CF aged less than 24 months (Trial 8). Of the 353 patients included in the pooled analyses of patients with CF who had either a G551D mutation or were homozygous for the F508del mutation in the CFTR gene, 50% of patients were female and 97% were Caucasian; 221 received KALYDECO, and 132 received placebo from 16 to 48 weeks. (…) The incidence of adverse reactions below is based upon two double-blind, placebo-controlled, 48-week clinical trials (Trials 1 and 2) in a total of 213 patients with CF ages 6 to 53 who have a G551D mutation in the CFTR gene and who were treated with KALYDECO 150 mg orally or placebo twice daily. Table 2 shows adverse reactions occurring in ≥8% of KALYDECO-treated patients with CF who have a G551D mutation in the CFTR gene that also occurred at a higher rate than in the placebo-treated patients in the two double-blind, placebo-controlled trials. (See Table 2) (…) **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** KALYDECO is indicated for the treatment of CF in pediatric patients 6 months to 17 years of age who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)].

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					Placebo-controlled clinical trials established efficacy and safety in the following pediatric patients with CF: • 6 to 17 years of age with a G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H mutation in the CFTR gene [see Adverse Reactions (6) and Clinical Studies (14)]. • 12 to 17 years of age who are heterozygous for the F508del mutation and a second mutation predicted to be responsive to ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)]. (…) **12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** *CFTR Chloride Transport Assay in Fisher Rat Thyroid (FRT) cells expressing mutant CFTR* In order to evaluate the response of mutant CFTR protein to ivacaftor, total chloride transport was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual CFTR mutations. Ivacaftor increased chloride transport in FRT cells expressing CFTR mutations that result in CFTR protein being delivered to the cell surface. Data shown in Figure 1 are the mean (n=3-7) net change over baseline in CFTR mediated chloride transport following the addition of ivacaftor in FRT cells expressing mutant CFTR proteins. The in vitro CFTR chloride response threshold was designated as a net increase of at least 10% of normal over baseline (dotted line) because it is predictive or reasonably expected to predict clinical benefit. Mutations with an increase in chloride transport of 10% or greater are considered responsive. A patient must have at least one CFTR mutation responsive to ivacaftor to be indicated. Mutations including F508del that are not responsive to ivacaftor potentiation, based on the in vitro CFTR chloride response threshold, are listed in Figure 1 below the dotted line. (see Figure 1) Note that splice mutations cannot be studied in this FRT assay and are not included in Figure 1. Evidence of clinical efficacy exists for non-canonical splice mutations 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G and E831X and these are listed in Table 3 below [see also Clinical Studies (14.4)]. The G970R mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor [see Clinical Studies (14.2)]. Ivacaftor also increased chloride transport in cultured human bronchial epithelial (HBE) cells derived from CF patients who carried F508del on one CFTR allele and either G551D or R117H-5T on the second CFTR allele. Table 3 lists mutations that are responsive to ivacaftor based on 1) a positive clinical response and/or 2) in vitro data in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal). (see Table 3) **12.2 Pharmacodynamics** Sweat Chloride Evaluation Changes in sweat chloride (a biomarker) response to KALYDECO were evaluated in seven clinical trials [see Clinical Studies (14)]. In a two-part, randomized, double-blind, placebo-controlled, crossover clinical trial in patients with CF who had a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene (Trial 4), the treatment difference in mean change in sweat chloride from baseline through 8 weeks of treatment was -49 mmol/L (95% CI -57, -41). The mean changes in sweat chloride for the mutations for which KALYDECO is indicated ranged from -51 to -8, whereas the range for individual subjects with the G970R mutation was -1 to -11 mmol/L. In an open-label clinical trial in 34 patients ages 2 to less than 6 years administered either 50 mg or 75 mg of ivacaftor twice daily (Trial 6), the mean absolute change from baseline in sweat chloride through 24 weeks of treatment was -45 mmol/L (95% CI -53, -38) [see Use in Specific Populations (8.4)]. In a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in patients with CF age 12 years and older who were heterozygous for the F508del mutation and with a second CFTR mutation predicted to be responsive to ivacaftor (Trial 7), the treatment difference in mean change in sweat chloride from study baseline to the average of Week 4 and Week 8 of treatment for KALYDECO treated patients was -4.5 mmol/L (95% CI -6.7, -2.3). In a 24-week, open-label clinical trial in patients with CF aged less than 24 months administered either 25 mg, 50 mg or 75 mg of ivacaftor twice daily (Trial 8), the mean absolute change from baseline in sweat chloride for patients aged 12 months to less than 24 months (n=10) was -73.5 mmol/L (95% CI -86.0, -61.0) at Week 24, and the mean absolute change from baseline in sweat chloride for patients aged 6 months to less than 12 months (n=6) was -58.6 mmol/L (95% CI -75.9, -41.3) at Week 24. [see Use in Specific Populations (8.4)]. (…) **14 CLINICAL STUDIES** **14.1 Trials in Patients with CF who have a G551D Mutation in the CFTR Gene** *Efficacy* The efficacy of KALYDECO in patients with CF who have a G551D mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving KALYDECO 150 mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study. (…) **14.2 Trial in Patients with a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R Mutation in the CFTR Gene** The efficacy and safety of KALYDECO in patients with CF who 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 39 patients with CF (Trial 4). Patients who completed Part 1 of this trial continued into the 16-week open-label Part 2 of the study. The mutations studied were G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. See Clinical Studies (14.1) for efficacy in patients with a G551D mutation. (See Table 6) (…) **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). (See Table 7) (…) **14.5 Trial in Patients Homozygous for the F508del Mutation in the CFTR Gene** Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV1 ≥40% predicted. (…) The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1. The treatment difference from placebo for the mean absolute change in percent predicted FEV1 through Week 16 in patients with CF homozygous for the

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

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					F508del mutation in the CFTR gene was 1.72 percentage points (1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively) and did not reach statistical significance (Table 9). (See Table 9) (…)
206038, 08/15/2018	**Ivacaftor and Lumacaftor**	Pulmonary	CFTR	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. *Limitations of Use* The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation. **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). In addition, the following clinical trials have been conducted: • A 24-week open-label trial (Trial 3) in 58 patients with CF aged 6 through 11 years homozygous for the F508del-CFTR mutation. • A 24-week, placebo-controlled trial (Trial 4) in 204 patients aged 6 through 11 years homozygous for the F508del-CFTR mutation. • A 24-week, open label trial (Trial 5) in 46 patients aged 12 years and older homozygous for the F508del-CFTR mutation and with advanced lung disease (ppFEV1 <40). • A 24-week, open-label trial (Trial 6) in 60 patients aged 2 through 5 years homozygous for the F508del-CFTR mutation. (…) Table 3 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 3) (…) The safety profile from two pediatric trials in CF patients aged 6 through 11 years who are homozygous for the F508del-CFTR mutation, a 24-week, open-label, multicenter Phase 3 safety trial in 58 patients (Trial 3) and a 24-week, placebo-controlled, Phase 3 clinical trial (Trial 4) in 204 patients (103 received lumacaftor 200 mg/ivacaftor 250 mg every 12 hours and 101 received placebo), was similar to that observed in Trials 1 and 2. Adverse reactions that are not listed in Table 3, and that occurred in ≥5% of lumacaftor/ivacaftor-treated patients with an incidence of ≥3% higher than placebo included: productive cough (17.5% vs 5.9%), nasal congestion (16.5% vs 7.9%), headache (12.6% vs 8.9%), abdominal pain upper (12.6% vs 6.9%), and sputum increased (10.7% vs 2.0%). In a 24-week, open-label, multicenter Phase 3 study in 60 patients aged 2 through 5 years with CF who are homozygous for the F508del-CFTR mutation (Trial 6) the safety profile was similar to that observed in studies in patients aged 6 years and older. **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** The efficacy of ORKAMBI in children ages 2 through 11 years is extrapolated from efficacy in patients ages 12 years and older homozygous for the F508del mutation in the CFTR gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 2 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. (…)
210491, 02/12/2018	**Ivacaftor and Tezacaftor**	Pulmonary	CFTR	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. **6 ADVERSE REACTIONS** (…) The safety profile for the CF patients enrolled in Trial 2 who were heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor was similar to that observed in Trials 1 and 3. **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** SYMDEKO is indicated for the treatment of CF in pediatric patients ages 12-17 years who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence [see Clinical Pharmacology (12.1) and Clinical Studies (14)]. Clinical trials included the following CF patients: • 12 to 17 years of age who are homozygous for the F508del mutation [see Adverse Reactions (6) and Clinical Studies (14)]. • 12 to 17 years of age who are heterozygous for the F508del mutation and a second mutation predicted to be

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Last Updated: 06/2019

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					responsive to tezacaftor/ivacaftor [see Adverse Reactions (6) and Clinical Studies (14)]. The safety and efficacy of SYMDEKO in patients with CF younger than 12 years of age have not been studied. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Effects on Sweat Chloride In Trial 1 (patients homozygous for the F508del mutation), the treatment difference between SYMDEKO and placebo in mean absolute change from baseline in sweat chloride through Week 24 was -10.1 mmol/L (95% CI: -11.4, -8.8). In Trial 2 (patients heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor), the treatment difference in mean absolute change from baseline in sweat chloride through Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) between SYMDEKO and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo. (…) **14 CLINICAL STUDIES** Dose Ranging: Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF (homozygous for the F508del mutation) 18 years of age and older with a screening ppFEV1≥40. In the study, 34 and 106 patients, respectively, received tezacaftor at once-daily doses of 10 mg, 30 mg, 100 mg, or 150 mg alone or in combination with ivacaftor 150 mg q12h, and 33 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean ppFEV1 change from baseline were observed with tezacaftor in combination with ivacaftor. Tezacaftor/ivacaftor in general had a greater mean treatment effect than tezacaftor alone. No additional benefit was observed at tezacaftor doses greater than 100 mg daily. Efficacy: The efficacy of SYMDEKO in patients with CF aged 12 years and older was evaluated in three Phase 3, double-blind, placebo-controlled trials (Trials1, 2, and 3). Trial 1 was a 24-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were homozygous for the F508del mutation in the CFTR gene. Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in CF patients who were heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Mutations predicted to be responsive were selected for the study based on the clinical phenotype (pancreatic sufficiency), biomarker data (sweat chloride), and in vitro responsiveness to tezacaftor/ivacaftor [see Clinical Studies (14.2)]. Patients were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo. Trial 3 was a 12-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro testing to tezacaftor and/or ivacaftor. (…) **14.1 Trial in Patients with CF Who Were Homozygous for the F508del Mutation in the CFTR Gene (Trial 1)** Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean ppFEV1 at baseline was 60.0% [range: 27.8% to 96.2%]. (see Table 8 and Figure 2) (…) **14.2 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 2)** Trial 2 evaluated 244 patients with CF aged 12 years and older (mean age 34.8 years). The mean ppFEV1 at baseline was 62.3% [range: 34.6 to 93.5]. Of the 244 patients included in the efficacy analysis, 146 patients had a splice mutation and 98 patients had a missense mutation as the second allele. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (see Table 9). In an analysis of BMI at Week 8, an exploratory endpoint, patients treated with SYMDEKO had a mean improvement of 0.2 kg/m2 [95% CI (0.0, 0.3)], 0.1 kg/m2 [95% CI (-0.1, 0.3)], and 0.3 kg/m2 [95% CI (0.1, 0.5)] versus placebo for the overall, splice, and missense mutation populations of patients, respectively. **14.3 Trial in Patients with CF Who Were Heterozygous for the F508del Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 3)** Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.1 years) who were heterozygous for the F508del mutation and had a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. CF patients with the F508del mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, CFTRdele2,3, 2183delAA>G, 2184insA, R1162X, R553X, 3659delC, 3905insT, G970R, I507del, R1066C, R347P, 1154insTC, 1811+1.6kbA>G, 2184delA, 405+1G>A, E60X, G85E, L1077P, Q39X, S466X, Y1092X, 1078delT, 1248+1G>A, 1677delTA, 1812-1G>A, 2869INSG, 3120+1G>A, 394delTT, 457TAT>G, 711+1G>T, 711+5G>A, 712-1G>T, G673x, L1065P, Q220X, Q493X, R709X, V520F. The mean ppFEV1 at baseline was 57.5% [range: 31.0 to 96.7]. The primary efficacy endpoint was change from baseline in absolute ppFEV1 through Week 12. The overall treatment difference between SYMDEKO and placebo for the mean absolute change in ppFEV1 from baseline through Week 12 was 1.2 percentage points (95% CI: -0.3, 2.6). This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.
211192, 05/02/2019	**Ivosidenib**	Oncology	IDH1	Indications and Usage, Dosage and Administration, Clinical	**1 INDICATIONS AND USAGE** **1.1 Newly-Diagnosed Acute Myeloid Leukemia** TIBSOVO is indicated for the treatment of newly-diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)]. **1.2 Relapsed or Refractory Acute Myeloid Leukemia**

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Pharmacology, Clinical Studies	TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of AML with TIBSOVO based on the presence of IDH1 mutations in the blood or bone marrow [see Clinical Studies (14.1)]. Patients without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse. Information on FDA-approved tests for the detection of IDH1 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Multiple doses of ivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies to levels similar to those observed at baseline in healthy subjects. In bone marrow, 2-HG concentrations were reduced by >90%. Cardiac Electrophysiology A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state Cmax following a 500 mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 136 patients with relapsed or refractory AML, who received TIBSOVO 500 mg daily [see Warnings and Precautions (5.1)]. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline. **14 CLINICAL STUDIES** **14.1 Newly-Diagnosed AML** The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) that included 28 adult patients with newly-diagnosed AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTimeTM IDH1 Assay. (See Table 6) (…) **14.2 Relapsed or Refractory AML** The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of 174 adult patients with relapsed or refractory AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTimeTM IDH1 Assay. (See Table 8) (…)
022065, 10/18/2011	**Ixabepilone (1)**	Oncology	ERBB2 (HER2)	Clinical Studies	**14 CLINICAL STUDIES** **Combination Therapy** (…) Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6. (…) **Monotherapy** HER2-positive patients must also have progressed during or after discontinuation of trastuzumab. In this study, the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 48% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%. (…)
022065, 10/18/2011	**Ixabepilone (2)**	Oncology	ESR, PGR (Hormone Receptor)	Clinical Studies	**14 CLINICAL STUDIES** **Combination Therapy** (…) Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2 negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6. (…) **Monotherapy** HER2-positive patients must also have progressed during or after discontinuation of trastuzumab. In this study, the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 48% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%. (…)
204839, 04/28/2016	**Lacosamide**	Neurology	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Special Populations* *CYP2C19 Polymorphism* There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. Results from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=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.

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Last Updated: 06/2019

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020406, 06/07/2018	**Lansoprazole**	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** **7.3 Tacrolimus** Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Drug-Drug Interactions* *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 PREVACID 30 mg (n=40), for nine days was conducted. (…)
022059, 12/06/2018	**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: • capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. *Limitation of Use:* Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine. • letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer. **2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dosing** *HER2-Positive Metastatic Breast Cancer* The recommended dose of TYKERB is 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended [see Clinical Pharmacology (12.3)]. Capecitabine should be taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs. *Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer* 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. (…) *Hormone Receptor-Positive, HER2+ Metastatic Breast Cancer:* In another randomized, Phase 3 clinical trial of postmenopausal patients (N = 355) with hormone receptor positive (HR+), HER2-positive metastatic breast cancer (MBC) which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies patients received TYKERB with trastuzumab and an aromatase inhibitor (AI) (letrozole, exemestane, or anastrozole), TYKERB with an AI, or trastuzumab with an AI. (…) *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**

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					Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (…) **14 CLINICAL STUDIES** **14.1 HER2-Positive Metastatic Breast Cancer** The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab. (…) (…) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab. (…) (…) Clinical Studies Describing Limitation of Use: In two randomized trials, TYKERB based chemotherapy regimens have been shown to be less effective than trastuzumab-based chemotherapy regimens. The first randomized, open-label study compared the safety and efficacy of 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/neo-adjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab. In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (See Table 8 and Figure 3) The efficacy and safety of TYKERB, in combination with an aromatase inhibitor (AI), were confirmed in another randomized Phase 3 trial. Patients enrolled were post-menopausal women who had hormone receptorpositive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior trastuzumabcontaining chemotherapy and endocrine therapies. (…) The study was designed to evaluate a potential benefit in Progression Free Survival (PFS) when double versus single HER2 targeted therapy was administered in combination with an AI (letrozole, exemestane, or anastrozole). The major efficacy outcome measure was PFS based on local radiology/investigator's assessment comparing TYKERB + trastuzumab + AI versus trastuzumab + AI. (…)
022059, 12/06/2018	**Lapatinib (2)**	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** TYKERB is indicated in combination with: (…) • 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. (…) **2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dosing** *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.

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Last Updated: 06/2019

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					6 ADVERSE REACTIONS **6.1 Clinical Trials Experience** (…) Hormone Receptor-Positive, Metastatic Breast Cancer: In a randomized clinical trial of patients (N = 1,286) with hormone receptor-positive, metastatic breast cancer, who had not received chemotherapy for their metastatic disease, patients received letrozole with or without TYKERB. (…) Hormone Receptor-Positive, HER2+ Metastatic Breast Cancer: In another randomized, Phase 3 clinical trial of postmenopausal patients (N = 355) with hormone receptor positive (HR+), HER2-positive metastatic breast cancer (MBC) which had progressed after prior trastuzumab-containing chemotherapy and endocrine therapies patients received TYKERB with trastuzumab and an aromatase inhibitor (AI) (letrozole, exemestane, or anastrozole), TYKERB with an AI, or trastuzumab with an AI. (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. (…) **14 CLINICAL STUDIES** **14.1 HER2-Positive Metastatic Breast Cancer** (…) Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. (…) **14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer** The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PgR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). (…) (…) In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 8 and Figure 3. (…) The efficacy and safety of TYKERB, in combination with an aromatase inhibitor (AI), were confirmed in another randomized Phase 3 trial. Patients enrolled were post-menopausal women who had hormone receptorpositive (HR+)/HER2-positive, metastatic breast cancer, which had progressed after prior trastuzumabcontaining chemotherapy and endocrine therapies. (…)
022059, 12/06/2018	**Lapatinib (3)**	Oncology	HLA-DQA1, HLA-DRB1	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 substudy 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 DRBI*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.
210861, 11/26/2018	**Larotrectinib**	Oncology	NTRK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that: • have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, (…) **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for treatment with VITRAKVI based on the presence of a NTRK gene fusion in tumor specimens [see Clinical Studies (14)]. An FDA-approved test for the detection of NTRK gene fusion is not currently available. **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** (…) NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Most adults (80%) received VITRAKVI 100 mg orally twice daily and 68% of pediatrics (18 years or younger) received VITRAKVI 100 mg/m2 twice daily up to a maximum dose of 100 mg twice daily. (…) **14 CLINICAL STUDIES** The efficacy of VITRAKVI was evaluated in pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials: Study LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). (…) (…) Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH). NTRK gene fusions were inferred in three patients with infantile fibrosarcoma who had a documented ETV6 translocation identified by FISH. (…)

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					(…) The assessment of efficacy was based on the first 55 patients with solid tumors with an NTRK gene fusion enrolled across the three clinical trials. (…) The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). A total of 50 patients had NTRK gene fusions detected by NGS and 5 patients had NTRK gene fusions detected by FISH. Efficacy results are summarized in Tables 4, 5, and 6.
205834, 11/09/2017	Ledipasvir and Sofosbuvir	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**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 Latino; mean body mass index was 28 kg/m^2 (range: 18 to 56 kg/m^2); 81% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 80% had genotype 1a HCV infection; 73% had non-C/C IL28B alleles (CT or TT). (…) *Treatment-Naïve Adults with or without Cirrhosis – ION-1 (Study 0102)* (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 865 treated subjects, the median age was 54 years (range: 18 to 80); 59% of the subjects were male; 85% were White; 12% were Black; 12% were Hispanic or Latino; mean body mass index was 27 kg/m^2 (range: 18 to 48 kg/m^2); 79% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 67% had genotype 1a HCV infection; 70% had non-C/C IL28B alleles (CT or TT); and 16% had cirrhosis. (…) *Previously-Treated Adults with or without Cirrhosis – ION-2 (Study 0109)* (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 440 treated subjects, the median age was 57 years (range: 24 to 75); 65% of the subjects were male; 81% were White; 18% were Black; 9% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 19 to 50 kg/m^2); 89% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; 79% had genotype 1a HCV infection; 88% had non-C/C IL28B alleles (CT or TT); and 20% had cirrhosis. Forty-seven percent (47%) of the subjects failed a prior therapy of pegylated interferon and ribavirin. Among these subjects, 49% were relapse/breakthrough and 51% were non-responder. Fifty-three percent (53%) of the subjects failed a prior therapy of pegylated interferon and ribavirin with an HCV protease inhibitor. Among these subjects, 62% were relapse/breakthrough and 38% were non-responder. (See Table 14) (…) *Previously-Treated Adults with Cirrhosis – SIRIUS (Study 0121)* (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomized subjects, the median age was 56 years (range: 23 to 77); 74% of the subjects were male; 97% were White; mean body mass index was 27 kg/m^2 (range: 19 to 47 kg/m^2); 63% had genotype 1a HCV infection; 94% had non-C/C IL28B alleles (CT or TT). One subject discontinued therapy while on placebo, and was not included in the efficacy analysis. (…) **14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1** (…) Of the 335 treated subjects, the median age was 52 years (range: 26 to 72); 82% of the subjects were male; 61% were White; 34% were Black; mean body mass index was 27 kg/m^2 (range: 18 to 66 kg/m^2); 75% had genotype 1a HCV infection; 2% had genotype 4 infection; 76% had non-C/C IL28B alleles (CT or TT); and 20% had compensated cirrhosis. Fifty-five percent (55%) of the subjects were treatment-experienced. (…) (…) SVR12 rates were 94% (63/67) in subjects with cirrhosis and 98% (46/47) in subjects who were previously-treated and had cirrhosis. The relapse rate in the ION-4 trial in Black subjects was 9% (10/115), all of whom were IL28B non-CC genotype, and none in non-Black subjects (0/220). In the ION-1, ION-2, and ION-3 HCV mono-infection studies, relapse rates were 3% (10/305) in Black subjects and 2% (26/1637) in non-Black subjects. (…)
021880, 05/28/2019	Lenalidomide	Hematology	Chromosome 5q	Boxed Warning, Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies	**BOXED WARNING** WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM *Hematologic Toxicity (Neutropenia and Thrombocytopenia)* REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [see Dosage and Administration (2.2)]. **1 INDICATIONS AND USAGE** **1.2 Myelodysplastic Syndromes** REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Myelodysplastic Syndromes* A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. 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 8 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 9 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease. (See Tables 9 and 10)

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Last Updated: 06/2019

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					8 USE IN SPECIFIC POPULATIONS **8.5 Geriatric Use** (…) Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. (…) **14 CLINICAL STUDIES** **14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality** The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. (…)
207988, 12/22/2015	Lesinurad	Rheumatology	CYP2C9	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** **7.1 CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 inducers** Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone), and in CYP2C9 poor metabolizers [see Clinical Pharmacology (12.3)]. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lesinurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, ZURAMPIC exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with CYP2C9 *2/*2 [N=1], and *3/*3 [N=1] genotype) compared to CYP2C9 extensive metabolizers (i.e., CYP2C9 *1/*1 [N=41] genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9 [see Drug Interactions (7.1)].
020726, 04/05/2018	Letrozole	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Adjuvant Treatment of Early Breast Cancer** Femara (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. **1.3 First and Second-Line Treatment of Advanced Breast Cancer** Femara is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy [see Clinical Studies (14.4, 14.5)]. **6 ADVERSE REACTIONS** **6.1 Adjuvant Treatment of Early Breast Cancer** (…) *Bone Study* Results of a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) bone mineral density (BMD) of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) (P<0.0001). (…) *Lipid Study* In a phase 3 safety trial in 262 postmenopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen. (…) **14 CLINICAL STUDIES** **14.1 Updated Adjuvant Treatment of Early Breast Cancer** In a multicenter study enrolling over 8,000 postmenopausal women with resected, receptor-positive early breast cancer, one of the following treatments was randomized in a double-blind manner (See Table 6) (…) **14.2 Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months** A double-blind, randomized, placebo-controlled trial of Femara was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease free after 5 years of adjuvant treatment with tamoxifen. (See Table 8) (…) (…) Table 9 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 9) (…) **14.4 First-Line Treatment of Advanced Breast Cancer** A randomized, double-blind, multinational trial compared Femara 2.5 mg with tamoxifen 20 mg in 916 postmenopausal patients with locally advanced (Stage IIIB or loco-regional recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial. (See Table 11) (…) (…) Table 13 shows results in the subgroup of women who had received prior antiestrogen adjuvant therapy, Table 14, results by disease site and Table 15, the results by receptor status. (…) **14.5 Second-Line Treatment of Advanced Breast Cancer**

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Last Updated: 06/2019

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					Femara was initially studied at doses of 0.1 mg to 5.0 mg daily in six non-comparative Phase I/II trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least antiestrogen therapy. (See Table 16) (…)
021451, 11/02/2018	**Lidocaine and Prilocaine (1)**	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
021451, 11/02/2018	**Lidocaine and Prilocaine (2)**	Anesthesiology	G6PD	Warnings and Precautions, Clinical Pharmacology	**5 WARNINGS AND PRECAUTIONS** **5.1 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…) **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)] (…)
021623, 11/02/2018	**Lidocaine and Tetracaine (1)**	Anesthesiology	G6PD	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
021623, 11/02/2018	**Lidocaine and Tetracaine (2)**	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions, Patient Counseling Information	**5 WARNINGS AND PRECAUTIONS** **5.1 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue SYNERA and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. **17 PATIENT COUNSELING INFORMATION** • Advise patients not to use SYNERA if they have a history of methemoglobinemia. • Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue. (…)
209229, 05/16/2018	**Lofexidine**	Anesthesiology	CYP2D6	Use in Specific Populations	**8 USE IN SPECIFIC POPULATIONS** **8.8 CYP2D6 Poor Metabolizers** Although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Clinical Pharmacology (12.3)].
210868, 11/02/2018	**Lorlatinib (1)**	Oncology	ALK	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** LORBRENA® is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on • crizotinib and at least one other ALK inhibitor for metastatic disease; or • alectinib as the first ALK inhibitor therapy for metastatic disease; or • ceritinib as the first ALK inhibitor therapy for metastatic disease. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience**

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					(…) The data in Warnings and Precautions reflect exposure to LORBRENA in 332 patients with ALK-positive or ROS1-positive, metastatic non small cell lung cancer (NSCLC) enrolled in a multi-cohort, multinational, non-comparative, dose-finding, and activity-estimating trial (Study B7461001) who received LORBRENA at doses ranging from 10 mg to 200 mg daily in single or divided doses. The data described below reflect exposure to LORBRENA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA 100 mg orally once daily in Study B7461001. (…) **14 CLINICAL STUDIES** **14.1 ALK-Positive Metastatic NSCLC Previously Treated with an ALK Kinase Inhibitor** The efficacy of LORBRENA was demonstrated in a subgroup of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK kinase inhibitors who were enrolled in a non-randomized, dose-ranging and activity-estimating, multi cohort, multicenter study (Study B7461001; NCT01970865). (…) (…) In addition, for patients with ALK-positive metastatic NSCLC, the extent and type of prior treatment was specified for each individual cohort (See Table 4). (…)
210868, 11/02/2018	Lorlatinib (2)	Oncology	ROS1	Adverse Reactions	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data in Warnings and Precautions reflect exposure to LORBRENA in 332 patients with ALK-positive or ROS1-positive, metastatic non small cell lung cancer (NSCLC) enrolled in a multi-cohort, multinational, non-comparative, dose-finding, and activity-estimating trial (Study B7461001) who received LORBRENA at doses ranging from 10 mg to 200 mg daily in single or divided doses. The data described below reflect exposure to LORBRENA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA 100 mg orally once daily in Study B7461001. (…)
210923, 07/31/2018	Lusutrombopag (1)	Hematology	F2 (Prothrombin)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210923, 07/31/2018	Lusutrombopag (2)	Hematology	F5 (Factor V Leiden)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210923, 07/31/2018	Lusutrombopag (3)	Hematology	PROC	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210923, 07/31/2018	Lusutrombopag (4)	Hematology	PROS1	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
210923, 07/31/2018	Lusutrombopag (5)	Hematology	SERPINC1 (Antithrombin III)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Thrombotic/Thromboembolic Complications** (…) Consider the potential increased thrombotic risk when administering MULPLETA to patients with known risk factors for thromboembolism, including genetic pro-thrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, MULPLETA should only be used if the potential benefit to the patient justifies the potential risk. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.
019832, 06/05/1998	Mafenide	Infectious Diseases	G6PD	Warnings, Adverse Reactions	**WARNINGS** Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate. **ADVERSE REACTIONS** (…) Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate. (…)

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Last Updated: 06/2019

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010721, 06/28/2019	**Meclizine**	Neurology	CYP2D6	Warnings and Precautions	**8 USE IN SPECIFIC POPULATIONS** **8.8 Genetic CYP2D6 Polymorphism** The genetic polymorphism of CYP2D6 that results in poor-, intermediate-, extensive-, and ultrarapid metabolizer phenotypes could contribute to large inter-individual variability in meclizine exposure. Therefore, when ANTIVERT® is administered to patients with CYP2D6 polymorphism, monitor for adverse reactions and clinical effect accordingly.
012250, 11/02/2018	**Mepivacaine (1)**	Anesthesiology	G6PD	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
012250, 11/02/2018	**Mepivacaine (2)**	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
205919, 02/20/2018	**Mercaptopurine (1)**	Oncology	TPMT	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/m^2) as a single daily dose. After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cellularity. 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. **2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency** Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]. *Homozygous deficiency in either TPMT or NUDT15* Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. *Heterozygous deficiency in TPMT and/or NUDT15* Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. **5 WARNINGS AND PRECAUTIONS** **5.1 Myelosuppression** The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia. Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)]. Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by coadministration with drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)]. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the 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 TMPT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					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)].
205919, 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/m^2) as a single daily dose. After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cellularity. 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. **2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency** Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]. *Homozygous deficiency in either TPMT or NUDT15* Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. *Heterozygous deficiency in TPMT and/or NUDT15* Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. **5 WARNINGS AND PRECAUTIONS** **5.1 Myelosuppression** The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia. Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)]. Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by coadministration with drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression [see Drug Interactions (7.1, 7.3 and 7.4)]. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see Warnings and Precautions (5.1)]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the 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 TMPT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient's actual TPMT activity [see Dosage and Administration (2.2) and Warnings and Precautions (5.1)].
204630, 05/21/2018	Methylene Blue	Hematology	G6PD	Contraindications, Warnings and Precautions	**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**

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

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					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 sulfa drugs such as dapsone. Monitor response to therapy with PROVAYBLUE™ through resolution of methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a response, consider additional treatment options [see Dosage and Administration (2.2)]. Patients with glucose-6-phosphate dehydrogenase deficiency may not reduce PROVAYBLUE™ to its active form in vivo. PROVAYBLUE™ may not be effective in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. **5.4 Hemolytic Anemia** Hemolysis can occur during treatment of methemoglobinemia with PROVAYBLUE™. Laboratory testing may show Heinz bodies, elevated indirect bilirubin and low haptoglobin, but the Coombs test is negative. The onset of anemia may be delayed 1 or more days after treatment with PROVAYBLUE™. The anemia may require red blood cell transfusions. [see Adverse Reactions (6.1)]. Use the lowest effective number of doses of PROVAYBLUE™ to treat methemoglobinemia. 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)].
017854, 08/29/2017	**Metoclopramide (1)**	Gastroenterology	CYB5R	Use in Specific Populations	**8 USE IN SPECIFIC POPULATIONS** **8.8 NADH-Cytochrome b5 Reductase Deficiency** Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal [see Overdosage (10)].
017854, 08/29/2017	**Metoclopramide (2)**	Gastroenterology	G6PD	Use in Specific Populations, Overdosage	**8 USE IN SPECIFIC POPULATIONS** **8.8 NADH-Cytochrome b5 Reductase Deficiency** Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal [see Overdosage (10)]. **10 OVERDOSAGE** (…) Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may be fatal. (…)
017854, 08/29/2017	**Metoclopramide (3)**	Gastroenterology	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.2 Dosage for Gastroesophageal Reflux** Reglan tablets may be administered continuously or intermittently in patients with symptomatic gastroesophageal reflux who fail to respond to conventional therapy: Continuous Dosing The recommended adult dosage of Reglan is 10 to 15 mg four times daily for 4 to 12 weeks. The treatment duration is determined by endoscopic response. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 60 mg. Table 1 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 1) **2.3 Dosage for Acute and Recurrent Diabetic Gastroparesis** The recommended adult dosage for the treatment of acute and recurrent diabetic gastroparesis is 10 mg four times daily for 2 to 8 weeks, depending on symptomatic response. Avoid Reglan treatment for greater than 12 weeks [see Warnings and Precautions (5.1)]. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 40 mg. Table 2 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors. (See Table 2) **8 USE IN SPECIFIC POPULATIONS** **8.9 CYP2D6 Poor Metabolizers** Metoclopramide is a substrate of CYP2D6. The elimination of metoclopramide may be slowed in patients who are CYP2D6 poor metabolizers (compared to patients who are CYP2D6 intermediate, extensive, or ultra-rapid metabolizers); possibly increasing the risk of dystonic and other adverse reactions to Reglan [see Clinical Pharmacology (12.3)]. Reduce the Reglan dosage in patients who are poor CYP2D6 metabolizers [see Dosage and Administration (2.2, 2.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Elimination Metabolism: Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monodeethylmetoclopramide, a major oxidative metabolite, is formed primarily by CYP2D6, an enzyme subject to genetic variability [see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.9)].

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Last Updated: 06/2019

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019962, 05/06/2014	Metoprolol	Cardiology	CYP2D6	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** **7.2 CYP2D6 Inhibitors** Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity [see Drug Interactions (7.2)].
207997, 06/21/2018	Midostaurin (1)	Oncology	FLT3	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Acute Myeloid Leukemia** RYDAPT is indicated, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by a FDA approved test [see Dosage and Administration (2.1), Clinical Studies (14.1)]. (…) **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of AML with RYDAPT based on the presence of FLT3 mutation positivity [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of FLT3 mutation in AML is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Acute Myeloid Leukemia* The safety evaluation of RYDAPT (50 mg twice daily with food) in patients with newly diagnosed FLT3 mutated AML is based on a randomized, double-blind, trial of RYDAPT (n=345) or placebo (n=335) with chemotherapy [see Clinical Studies (14.1)] (…) (…) Table 2 presents the frequency category of adverse reactions reported in the randomized trial in patients with newly diagnosed FLT3 mutated AML. Adverse reactions are listed according to body system. Within each body system, the adverse reactions are ranked by frequency, with the most frequent reactions first. Table 3 presents the key laboratory abnormalities from the same randomized trial in patients with newly diagnosed FLT3 mutated AML. (See Table 2) (…) **14 CLINICAL STUDIES** **14.1 Acute Myeloid Leukemia** *Study 1* RYDAPT in combination with chemotherapy was investigated in a randomized, double-blind placebo-controlled trial of 717 patients with newly-diagnosed FLT3-mutated AML. In this study, FLT3 mutation status was determined prospectively with a clinical trial assay and verified retrospectively using the companion diagnostic LeukoStrat® CDx FLT3 Mutation Assay, which is an FDA-approved test for selection of patients with AML for RYDAPT treatment. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio less than 0.7, and ITD with allelic ratio greater than or equal to 0.7. (…) (…) The randomized patients had a median age of 47 years (range, 18-60 years), 44% were male, and 88% had a performance status of 0-1. AML was de novo onset in 95%. The percentage of patients with FLT3-ITD allelic ratio < 0.7, FLT3-ITD allelic ratio ≥ 0.7, and FLT3-TKD mutations were identical (per randomized FLT3 stratum) on both arms (48%, 30%, and 23%, respectively). (…).
207997, 06/21/2018	Midostaurin (2)	Oncology	NPM1	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Acute Myeloid Leukemia** *Study 1* (…) Of the 563 patients with NPM1 testing, 58% had an NPM1 mutation. The two treatment groups were generally balanced with respect to the baseline demographics and disease characteristics, except that the placebo arm had a higher percentage of females (59%) than in the midostaurin arm (52%). NPM1 mutations were identified in 55% of patients tested on the midostaurin arm and 60% of patients tested on the placebo arm. (…)
207997, 06/21/2018	Midostaurin (3)	Oncology	KIT	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Systemic Mastocytosis** *Study 2* (…) Of the 116 patients treated, a study steering committee identified 89 patients who had measurable C-findings and were evaluable for response. The median age in this group was 64 years (range: 25 to 82), 64% of patients were male, and nearly all patients (97%) were Caucasian. Among these patients, 36% had prior therapy for SM, and 82% had the KIT D816V mutation detected at baseline. Their median duration of treatment was 11 months (range: < 1 to 68 months), with treatment ongoing in 17%. Efficacy was established on the basis of confirmed complete remission (CR) plus incomplete remission (ICR) by 6 cycles of RYDAPT by modified Valent criteria for ASM and SM-AHN (Table 7). Table 7 shows responses to RYDAPT according to modified Valent criteria. Confirmed major or partial responses occurred in

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					46 of 73 patients with a documented KIT D816V mutation, 7 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. (…)
208623, 08/10/2018	Migalastat	Inborn Errors of Metabolism	GLA	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** GALAFOLD™ is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data [see Clinical Pharmacology (12.1)]. (…) **2 DOSAGE AND ADMINISTRATION** • Select adults with confirmed Fabry disease who have an amenable GLA variant for treatment with GALAFOLD [see Table 2 in Clinical Pharmacology (12.1)]. • Treatment is indicated for patients with an amenable GLA variant that is interpreted by a clinical genetics professional as causing Fabry disease (pathogenic, likely pathogenic) in the clinical context of the patient. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease). (…) **12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** In Vitro Amenability Assay In an in vitro assay (HEK-293 assay), Human Embryonic Kidney (HEK-293) cell lines were transfected with specific GLA variants (mutations) which produced mutant alpha-Gal A proteins. In the transfected cells, amenability of the GLA variants was assessed after a 5-day incubation with 10 micromol/L migalastat. A GLA variant was categorized as amenable if the resultant mutant alpha-Gal A activity (measured in the cell lysates) met two criteria: 1) it showed a relative increase of at least 20% compared to the pre-treatment alpha-Gal A activity, and 2) it showed an absolute increase of at least 3% of the wild-type (normal) alpha-Gal A activity. The in vitro assay did not evaluate trafficking of the mutant alpha-Gal A proteins into the lysosome or the dissociation of migalastat from the mutant alpha-Gal A proteins within the lysosome. Also, the in vitro assay did not test whether a GLA variant causes Fabry disease or not. The GLA variants which are amenable to treatment with GALAFOLD, based on the in vitro assay data, are shown in Table 2. Inclusion of GLA variants in this table does not reflect interpretation of their clinical significance in Fabry disease. Whether a certain amenable GLA variant in a patient with Fabry disease is disease-causing or not should be determined by the prescribing physician (in consultation with a clinical genetics professional, if needed) prior to treatment initiation. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease). (See Table 2) If a GLA variant does not appear in Table 2, it is either non-amenable (if tested) or has not been tested for in vitro amenability. For further information, please contact Amicus Medical Information at 1-877-4AMICUS or medinfousa@amicusrx.com. **12.2 Pharmacodynamics** In Study 1, 31 of 50 patients with amenable GLA variants (18 on GALAFOLD, 13 on placebo) had lyso-Gb3 assessments available after 6 months of treatment. (…) (…) In Study 2, 46 of 56 patients with amenable GLA variants (31 on GALAFOLD, 15 on enzyme replacement therapy (ERT)) had lyso-Gb3 assessments available after 18 months of treatment. The median change from baseline to month 18 in plasma lyso-Gb3 (nmol/L) was 0.53 (range -2.27, 28.3) in patients on GALAFOLD and -0.03 (range -11.9, 2.57) in patients on ERT. **14 CLINICAL STUDIES** (…) Of the 67 enrolled patients, 50 patients (32 females, 18 males) had amenable GLA variants based on the in vitro amenability assay [see Clinical Pharmacology (12.1)]. (See Table 3) In Study 1, patients with non-amenable GLA variants (n = 17) had no change from baseline in the average number of GL-3 inclusions per KIC after 6 months of treatment.
202611, 04/27/2018	Mirabegron	Urology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although in vitro studies suggest a role for CYP2D6 and 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 16% and 17% higher than in extensive metabolizers of CYP2D6, respectively. In vitro and ex vivo studies have shown the involvement of butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.
020098, 07/26/2018	Mivacurium	Anesthesiology	BCHE	Warnings, Precautions, Clinical Pharmacology	**WARNINGS** **Administration** MIVACRON is metabolized by plasma cholinesterase and should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene. **PRECAUTIONS** **Reduced Plasma Cholinesterase Activity**

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Last Updated: 06/2019

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					The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiophate, and certain antineoplastic drugs). MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.1 to 0.2 mg/kg MIVACRON, the clinically effective duration of action was 8 minutes to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients. As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (one in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED10-20 in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient. **CLINICAL PHARMACOLOGY** **Pharmacodynamics** Administration of MIVACRON over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see PRECAUTIONS - Reduced Plasma Cholinesterase Activity and CLINICAL PHARMACOLOGY - Individualization of Dosages subsection). **Individualization of Dosages** **Reduced Plasma Cholinesterase Activity** The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of MIVACRON are not recommended in homozygous patients. MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After an initial dose of 0.15 mg/kg MIVACRON, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotype and normal plasma cholinesterase activity. Lower infusion rates of MIVACRON are recommended in these patients (see PRECAUTIONS - Reduced Plasma Cholinesterase Activity).
020717, 01/15/2015	Modafinil	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Interactions with CNS Active Drugs* CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine and desipramine) and selective serotonin reuptake inhibitors that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased. PROVIGIL may cause elevation of the levels of the tricyclics in this subset of patients [see Drug Interactions (7)]. (…)
050791, 10/27/2015	Mycophenolic Acid	Transplantation	HPRT1	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.10 Rare Hereditary Deficiencies** Myfortic is an inosine monophosphate dehydrogenase inhibitor (IMPDH Inhibitor). Myfortic should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease including renal failure.
014214, 11/28/2012	Nalidixic Acid	Infectious Diseases	G6PD	Precautions, Adverse Reactions	**PRECAUTIONS** (…) Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS) (…) **ADVERSE REACTIONS** (…) Tendon disorders including tendon rupture, cholestasis, paresthesia, metabolic acidosis, thrombocytopenia, leukopenia, or hemolytic anemia, sometimes associated with glucose 6- phosphate dehydrogenase deficiency and peripheral neuropathy. (See WARNINGS) (…)
021742, 11/30/2017	Nebivolol	Cardiology	CYP2D6	Dosage and Administration, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.2 Subpopulations** *CYP2D6 Polymorphism* No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers [see Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics**

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Last Updated: 06/2019

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					Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity. Plasma levels of d–nebivolol increase in proportion to dose in EMs and PMs for doses up to 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-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.
076037, 07/17/2014	Nefazodone	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Cardiovascular-Active Drugs* *Digoxin* When nefazodone (200 mg BID) and digoxin (0.2 mg QD) were coadministered for 9 days to healthy male volunteers (n = 18) who were phenotyped as CYP2D6 extensive metabolizers, Cmax, Cmin, and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Digoxin had no effects on the pharmacokinetics of nefazodone and its active metabolites. Because of the narrow therapeutic index of digoxin, caution should be exercised when nefazodone and digoxin are coadministered; plasma level monitoring for digoxin is recommended. *Propranolol* The coadministration of nefazodone (200 mg BID) and propranolol (40 mg BID) for 5.5 days to healthy male volunteers (n = 18), including 3 poor and 15 extensive CYP2D6 metabolizers, resulted in 30% and 14% reductions in Cmax and AUC of propranolol, respectively, and a 14% reduction in Cmax for the metabolite, 4-hydroxypropranolol. The kinetics of nefazodone, hydroxynefazodone, and triazole-dione were not affected by coadministration of propranolol. However, Cmax, Cmin, and AUC of m-chlorophenylpiperazine were increased by 23%, 54%, and 28%, respectively. No change in initial dose of either drug is necessary and dose adjustments should be made on the basis of clinical response. *CYP2D6 Isozyme* A subset (3% to 10%) of the population has reduced activity of the drug-metabolizing enzyme CYP2D6. Such individuals are referred to commonly as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. The pharmacokinetics of nefazodone and its major metabolites are not altered in these "poor metabolizers." Plasma concentrations of one minor metabolite (mCPP) are increased in this population; the adjustment of nefazodone dosage is not required when administered to "poor metabolizers." Nefazodone and its metabolites have been shown in vitro to be extremely weak inhibitors of CYP2D6. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme.
208051, 06/28/2018	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)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** ExteNET The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2- positive early-stage breast cancer. (…) **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 after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer. A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). (…)
208051, 06/28/2018	Neratinib (2)	Oncology	ESR, PGR (Hormone Receptor)	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Extended Adjuvant Treatment in Breast Cancer** (…) A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). Randomization was stratified by the following factors: hormone receptor status, nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. (…) (…) Fifty-seven percent (57%) had hormone receptor positive disease (defined as ER-positive and/or PgR-positive), 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. (See Table 9) (…)
022068, 08/21/2018	Nilotinib (1)	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in	**1 INDICATIONS AND USAGE** **1.1 Adult and Pediatric Patients with Newly Diagnosed Ph+ CML-CP** Tasigna (nilotinib) is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. **1.2 Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP** Tasigna is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib. **1.3 Pediatric Patients with Resistant or Intolerant Ph+ CML-CP**

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Last Updated: 06/2019

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				Specific Populations, Clinical Pharmacology, Clinical Studies	Tasigna is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy. **2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dosing** *Dosage in Adult Patients with Newly Diagnosed Ph+ CML-CP* The recommended dose of Tasigna is 300 mg orally twice daily. *Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP* The recommended dose of Tasigna is 400 mg orally twice daily. *Dosage in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP* The recommended dose of Tasigna for pediatric patients is 230 mg/m2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs. **2.2 Discontinuation of treatment after a sustained molecular response (MR4.5) on Tasigna** *Patient Selection* *Eligibility for Discontinuation of Treatment* Ph+ CML-CP patients with typical BCR-ABL transcripts who have been taking Tasigna for a minimum of 3 years and have achieved a sustained molecular response (MR4.5, corresponding to = BCR-ABL/ABL ≤ 0.0032% IS) may be eligible for treatment discontinuation [see Clinical Studies (14.3, 14.4)]. Information on FDA authorized tests for the detection and quantitation of BCR-ABL transcripts to determine eligibility for treatment discontinuation is available at http://www.fda.gov/CompanionDiagnostics. Patients with typical BCR-ABL transcripts (i.e., 13a2/b2a2 or e14a2/b3a2) who achieve the sustained MR4.5 criteria are eligible for discontinuation of Tasigna treatment. Patients must continue to be monitored for possible loss of molecular remission after treatment discontinuation. Use the same FDA authorized test to consistently monitor molecular response levels while on and off treatment. Consider discontinuation of treatment in patients with newly diagnosed Ph+ CML-CP who have: • been treated with Tasigna for at least 3 years • maintained a molecular response of at least MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01% IS) for one year prior to discontinuation of therapy • achieved an MR4.5 for the last assessment taken immediately prior to discontinuation of therapy • been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2) • no history of accelerated phase or blast crisis • no history of prior attempts of treatment-free remission discontinuation that resulted in relapse. Consider discontinuation of treatment in patients with Ph+ CML-CP that are resistant or intolerant to treatment with imatinib who have achieved a sustained molecular response (MR4.5) on Tasigna who have: • been treated with Tasigna for a minimum of 3 years • been treated with imatinib only prior to treatment with Tasigna • achieved a molecular response of MR4.5 (corresponding to = BCR-ABL/ABL ≤ 0.0032% IS) • sustained an MR4.5 for a minimum of one year immediately prior to discontinuation of therapy • been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2) • no history of accelerated phase or blast crisis • no history of prior attempts of treatment-free remission discontinuation that resulted in relapse. Monitor BCR-ABL transcript levels and complete blood count with differential in patients who have discontinued Tasigna therapy monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter [see Warnings and Precautions (5.16)]. Upon the loss of MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01%IS) during the treatment-free phase, monitor BCR-ABL transcript levels every 2 weeks until BCR-ABL levels remain lower than major molecular response (MMR, corresponding to MR3.0 or = BCR-ABL/ABL ≤ 0.1%IS) for 4 consecutive measurements. The patient can then proceed to the original monitoring schedule. **2.3 Reinitiation of treatment in patients who lose molecular response after discontinuation of therapy with Tasigna.** • Newly diagnosed patients who lose MMR must reinitiate treatment within 4 weeks at the dose level prior to discontinuation of therapy [see Warnings and Precautions (5.16)]. Patients who reinitiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until major molecular response is re-established and every 12 weeks thereafter. • Patients resistant or intolerant to prior treatment that included imatinib with confirmed loss of MR4.0 (2 consecutive measures separated by at least 4 weeks showing loss of MR4.0) or loss of MMR must reinitiate treatment within 4 weeks at the dose level prior to discontinuation of therapy [see Warnings and Precautions (5.16)]. Patients who reinitiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4.0 is re-established and every 12 weeks thereafter. **2.4 Dosage Modification for QT Interval Prolongation** See Table 2 for dose adjustments for QT interval prolongation [see Clinical Pharmacology (12.2)]. (See Table 2) (…) **2.7 Dosage Modification for Hepatic Impairment** If possible, consider alternative therapies. If Tasigna must be administered to patients with hepatic impairment, consider the following dose reduction: (See Table 6) (…) **2.8 Dosage Modification with Concomitant Strong CYP3A4 Inhibitors**

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					Avoid the concomitant use of strong CYP3A4 inhibitors. Should treatment with any of these agents be required, interrupt therapy with Tasigna. If patients must be coadministered a strong CYP3A4 inhibitor, reduce dosage to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP. (…) **5 WARNINGS AND PRECAUTIONS** **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. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *In Adult Patients with Newly Diagnosed Ph+ CML-CP* The data below reflect exposure to Tasigna from a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the Tasigna 300 mg twice daily group was 61 months (range 0.1 to 71 months). The median actual dose intensity was 593 mg/day in the Tasigna 300 mg twice daily group. (…) (…) *In Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP* In the single open-label multicenter clinical trial, a total of 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP=321; CMLAP=137) at the recommended dose of 400 mg twice daily. (…) *Most Frequently Reported Adverse Reactions* Tables 7 and 8 show the percentage of adult patients experiencing non-hematologic adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in greater than 10% of adult patients who received at least 1 dose of Tasigna are listed. (See Tables 7 and 8) (…) *Laboratory Abnormalities* Table 9 shows the percentage of adult patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna. (See Table 9) (…) *Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)* The rate of musculoskeletal symptoms decreased in patients who entered the Tasigna treatment reinitiation (NTRI) phase, at 11/88 (12.5%) in the newly diagnosed population and 14/56 (25%) in the population previously treated with imatinib. Other adverse reactions observed in the Tasigna re-treatment phase were similar to those observed Tasigna use in patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP. (See Table 10) (…) **Additional Data from Clinical Trials** The following adverse drug reactions were reported in adult patients in the Tasigna clinical studies at the recommended doses. These adverse drug reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (greater than or equal to 1% and less than 10%), uncommon (greater than or equal to 0.1% and less than 1%), and unknown frequency (single events). For laboratory abnormalities, very common events (greater than or equal to 10%), which were not included in Tables 7 and 8, are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category, obtained from 2 clinical studies: 1. Adult patients with newly diagnosed Ph+ CML-CP 60 month analysis and, 2. Adult patients with resistant or intolerant Ph+ CML-CP and CMP-AP 24 months' analysis. (…) *In Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP* The data below reflect exposure to Tasigna from two studies in pediatric patients from 2 to less than 18 years of age with either newly diagnosed Ph+ CML-CP or imatinib/dasatinib resistant or intolerant Ph+ CML-CP treated at the recommended dose of 230 mg/m2 twice daily (n=69) [see Clinical Studies (14.5)]. The median time on treatment with Tasigna was 13.8 months (range: 0.7 to 30.9 months). The median actual dose intensity was 435.5 mg/m2 /day (range: 149 to 517 mg/m2 /day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%. In pediatric patients with Ph+ CML-CP, the most common (greater than 20%) non-hematologic adverse drug reactions were headache, rash, hyperbilirubinemia, alanine aminotransferase increased, pyrexia, nausea, upper respiratory tract infection, aspartate aminotransferase increased, and vomiting. The most common (greater than 5%) Grade 3/4 non-hematologic adverse drug reactions were alanine aminotransferase increased and hyperbilirubinemia. (…) **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** The safety and effectiveness of Tasigna have been established in pediatric patients greater than or equal to 1 year of age with newly diagnosed and resistant or intolerant Ph+ CML in chronic phase [see Clinical Studies (14.5)]. There are no data for pediatric patients under 2 years of age. Use of Tasigna in pediatric patients 1 to less than 2 years of age is supported by efficacy in pediatric patients 2 to 6 years of age. Use of Tasigna in pediatric patients 1 to less than 18 years of age is supported by evidence from two clinical trials [see Clinical Studies (14.5)]. The 25 patients with newly diagnosed Ph+ CML-CP were in the following age groups: 6 children (age 2 to less than 12 years) and 19 adolescents (age 12 to less than 18 years).

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					The 44 patients with resistant or intolerant Ph+ CML-CP included 18 children (age 2 to less than 12 years) and 26 adolescents (age 12 to less than 18 years). (…) **8.5 Geriatric Use** In the clinical trials of Tasigna (patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP), approximately 12% and 30% of patients were 65 years or over respectively. • Patients with newly diagnosed Ph+ CML-CP: There was no difference in major molecular response between patients aged less than 65 years and those greater than or equal to 65 years. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once or twice daily dosing. In adult patients with resistant or intolerant Ph+ CML given Tasigna 400 mg twice daily, the steady-state mean (%CV) Cmax and AUC0-12h were 2260 ng/ml (35%) and 18000 ng·h/ml (33%), respectively. In adult patients with newly diagnosed Ph+ CML given Tasigna 300 mg twice daily, the steady-state mean (%CV) Cmax and AUC0-12h were 1540 ng/ml (48%) and 13337 ng·h/ml (46%), respectively. (…) 12.3 Pharmacokinetics Specific Populations Age, sex, race/ethnicity, or body weight did not significantly affect the pharmacokinetics of nilotinib. The effect of renal impairment on nilotinib pharmacokinetics is unknown. *Pediatric Patients* Following administration of the approved recommend pediatric dosage of nilotinib, steady-state exposure of nilotinib were within 2-fold to adult patients treated with 400 mg twice daily. Steady-state Cmin was comparable across all age groups (pediatric patients from ages 2 to less than 18 years), diseases (patients with newly diagnosed and resistant or intolerant Ph+ CML) and studies. Body surface area correlated with nilotinib clearance and was the primary factor responsible for the PK differences between pediatrics and adults. **14 CLINICAL STUDIES** **14.1 Adult Newly Diagnosed Ph+ CML-CP** The ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials-Newly Diagnosed patients) study (NCT00471497) was an open-label, multicenter, randomized trial conducted to determine the efficacy of Tasigna versus imatinib tablets in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within 6 months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. Efficacy was based on a total of 846 patients: 283 patients in the imatinib 400 mg once daily group, 282 patients in the Tasigna 300 mg twice daily group, 281 patients in the Tasigna 400 mg twice daily group. (…) The primary efficacy endpoint was major molecular response (MMR) at 12 months after the start of study medication. MMR was defined as less than or equal to 0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a greater than or equal to 3 log reduction of BCR-ABL transcript from standardized baseline. Efficacy endpoints are summarized in Table 12. (See Table 12) (…) **14.2 Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP** Study CAMN107A2101 (referred to as Study A2101) (NCT00109707) was a single-arm, open-label, multicenter study conducted to evaluate the efficacy and safety of Tasigna (400 mg twice daily) in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic and accelerated phase disease. The definition of imatinib resistance included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance was defined as discontinuation of treatment due to toxicity and lack of a major cytogenetic response at time of study entry. At the time of data cutoff, 321 patients with CML-CP and 137 patients with CML-AP with a minimum follow-up of 24 months were enrolled. In this study, about 50% of CML-CP and CML-AP patients were males, over 90% (CML-CP) and 80% (CML-AP) were Caucasian, and approximately 30% were age 65 years or older. **14.3 Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5)** The ENESTfreedom (Evaluating Nilotinib Efficacy and Safety in clinical Trials-freedom) study (NCT01784068) is an open-label, multicenter, single-arm study, where 215 adult patients with Ph+ CML-CP treated with Tasigna in first-line for ≥ 2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 190 patients (88.4%) entered the "Treatment-free Remission" (TFR) phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criteria: • The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL/ABL ≤ 0.01% IS), and maintained for 1 year • The last assessment being MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) • No more than two assessments falling between MR4 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤ 0.01% IS). The median age of patients who entered the TFR phase was 55 years, 49.5% were females, and 21.1% of the patients were ≥ 65 years of age. BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points: • Loss of MMR requiring patient to reinitiate Tasigna treatment • When the BCR-ABL levels returned to a range between MR4.0 and MR4.5 • When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0). **14.4 Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained molecular response (MR4.5) on Tasigna following prior imatinib therapy**

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

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					The ENESTop (Evaluating Nilotinib Efficacy and Safety in clinical Trials-STop) study (NCT01698905) is an open-label, multicenter, single-arm study, where 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for ≥ 3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to Tasigna, then switched to Tasigna for at least 2 years), and who achieved MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx ™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained molecular response (MR4.5) during the consolidation phase, defined by the following criterion: • The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤ 0.0032% IS) during 1 year. (…) Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL > 0.01% IS were considered having a confirmed loss of MR4.0, triggering reinitiation of Tasigna treatment. Patients with loss of MMR in the TFR phase immediately restarted Tasigna treatment without confirmation. All patients who restarted Tasigna therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks. (…) **14.5 Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP** The safety and efficacy of Tasigna in pediatric patients with Ph+ CML-CP have been investigated in two studies: Study CAMN107A2120 (NCT01077544), an open-label, single-arm, multi-center study that evaluated the pharmacokinetics, safety, and preliminary efficacy of Tasigna in pediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib (n=11), and Study CAMN107A2203 (NCT01844765), an open-label, single-arm, multi-center study evaluating the efficacy and safety of Tasigna in pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib (n=33) and newly diagnosed Ph+ CML-CP (n=25). In both studies, patients received Tasigna treatment at a dose of 230 mg/m2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). Data was pooled from a total of 69 pediatric patients (from 2 to less than 18 years of age) with either newly diagnosed Ph+ CML-CP (n=25; 6 children from 2 to less than 12 years and 19 adolescents from 12 to less than 18 years) or imatinib/dasatinib resistant or intolerant Ph+ CMLCP (n=44; 18 children from 2 to less than 12 years and 26 adolescents from 12 to less than 18 years). The median time on treatment with Tasigna was 13.80 months (range: 0.7 to 30.9 months). In patients with resistant or intolerant CML, the major molecular response (MMR; BCR-ABL/ABL ≤0.1% IS) rate was 40.9% (18/44, 95% CI: 26.3%, 56.8%) at 12 cycles (28 days per cycle). In patients with newly diagnosed CML, the MMR rate was 60.0% (15/25, 95% CI: 38.7%, 78.9%) at 12 cycles. In patients with resistant or intolerant CML, the cumulative MMR rate was 47.7% (21/44) by cycle 12. In patients with newly diagnosed CML, the cumulative MMR rate was 64.0% (16/25) by cycle 12. Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, the median time to first MMR was 2.8 months (range: 0.0 to 11.3). For the 17 patients with newly diagnosed CML who achieved MMR, the median time to first MMR was 5.6 months (range: 2.7 to 16.6). Among patients with resistant or intolerant CML, 4.5% of patients achieved BCR-ABL/ABL ≤0.0032% IS (MR4.5) by the cut-off date. Among patients with newly diagnosed CML, the percentage of patients who achieved MR4.5 was 28.0%. (See Table 13) (…)
022068, 08/21/2018	Nilotinib (2)	Oncology	UGT1A1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **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)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. However, the largest increases in bilirubin were observed in the (TA)7/(TA)7 genotype (UGT1A1*28) patients [see Warnings and Precautions (5.6)].
208447, 03/27/2017	Niraparib	Oncology	BRCA	Clinical Studies	**14 CLINICAL STUDIES** (…) Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline BRCA mutations (gBRCAm) were assigned to the germline BRCA mutated (gBRCAmut) cohort (n=203), and those without germline BRCA mutations were assigned to the non-gBRCA mut cohort (n=350). (…) The trial demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the gBRCA mut cohort and the non-gBRCA mut cohort (See Table 6, Figures 1 and 2).
009175, 11/04/2013	Nitrofurantoin	Infectious Diseases	G6PD	Warnings, Adverse Reactions	**WARNINGS** *Hemolytic anemia* Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphatedehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn. **ADVERSE REACTIONS** *Laboratory Adverse Events* The following laboratory adverse events have been reported with the use of nitrofurantoin; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see Warnings), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

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Last Updated: 06/2019

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125554, 05/02/2019	**Nivolumab (1)**	Oncology	BRAF	Adverse Reactions, Clinical Studies	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Unresectable or Metastatic Melanoma* *Previously Treated Metastatic Melanoma* (…) In CHECKMATE-037, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (...) *Previously Untreated Metastatic Melanoma* CHECKMATE-066 The safety of OPDIVO was also evaluated in Trial 4, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m2 every 3 weeks (n=205) [see Clinical Studies (14.1)]. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. (…) **14 CLINICAL STUDIES** **14.1 Unresectable or Metastatic Melanoma** *Previously Treated Metastatic Melanoma* (…) Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. (…) (…) Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%). (…) (…) There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. *Previously Untreated Metastatic Melanoma* *CHECKMATE-066* CHECKMATE-066 was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. (…) *CHECKMATE-067* (…) Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). (…) (…) Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%). (…) **14.2 Adjuvant Treatment of Melanoma** (…) Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥ 5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%). (…)
125554, 05/02/2019	Nivolumab (2)	Oncology	CD274 (PD-L1)	Clinical Pharmacology, Clinical Studies	**12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Specific Populations:* The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment. **14 CLINICAL STUDIES** **14.1 Unresectable or Metastatic Melanoma** *Previously Untreated Metastatic Melanoma* *CHECKMATE-066* (…) Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). (…) (…) Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma 44 Reference ID: 4198384 (11%), elevated LDH level (37%), PD-L1 greater than or equal to 5% tumor cell membrane expression (35%), and history of brain metastasis (4%). (…) *CHECKMATE-067* (…) Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). (…) (…) A total of 945 patients were randomized, 314 patients to the OPDIVO plus ipilimumab arm, 316 to the OPDIVO arm, and 315 to the ipilimumab arm. The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%). (…) (…) Figures 3 and 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx assay. Tumor samples were available for retrospective assessment for 97% of the study population; PD-L1 expression status was ascertained for 89% of the study population while in 6% of patients, melanin precluded evaluation of PD-L1 expression status. PD-L1 expression status was unknown for 5% of the study population due to consent withdrawal or missing samples. (see Figures 3 and 4) The data presented in the figure below summarize the results of exploratory analyses comparing the two OPDIVO-containing arms in subgroups defined by PD-L1 tumor expression. (see Figure 5) (…)

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Last Updated: 06/2019

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					14.2 Adjuvant Treatment of Melanoma *CHECKMATE-238* *(…)* Randomization was stratified by PD-L1 status (positive [based on 5% level] vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c). (…) (…) Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥ 5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%). (…) **14.3 Metastatic Non-Small Cell Lung Cancer (NSCLC)** *Second-line Treatment of Metastatic Squamous NSCLC* *CHECKMATE-017* (…) This study included patients regardless of their PD-L1 status. (…) (…) Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the study population, 17% (47/272) of patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% (106/225) had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1, and 53% (119/225) had PD-L1 positive squamous NSCLC, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive NSCLC subgroup. (…) *Second-line Treatment of Metastatic Non-Squamous NSCLC* *CHECKMATE-057* (…) The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression. (…) (…) Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (209/455) PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% (65/246) 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 Small Cell Lung Cancer** CHECKMATE-032 (NCT01928394) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic solid tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinumbased chemotherapy to receive treatment with OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. (…) **14.5 Advanced Renal Cell Carcinoma** *Previously Treated Renal Cell Carcinoma* CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior antiangiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. (…) (…) OS benefit was observed regardless of PD-L1 expression level. (See Table 28) (…) *Previously Untreated Renal Cell Carcinoma* CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. (…) (…) OS benefit was observed regardless of PD-L1 expression level. (See Table 29) (…) Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT. CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort study in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation study that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. (…) **14.6 Classical Hodgkin Lymphoma** Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT. CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance <40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity. (…) **14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** *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 PDL1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified

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Last Updated: 06/2019

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					exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup. **14.8 Urothelial Carcinoma** *CHECKMATE-275* (…) Patients were included regardless of their PD-L1 status. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients, were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 27. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%). (see Table 35)
125554, 05/02/2019	**Nivolumab (3)**	Oncology	Microsatellite Instability, Mismatch Repair	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** **1.8 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer** OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.9)]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials. **2 DOSAGE AND ADMINISTRATION** **2.1 Recommended Dosage** The recommended dosages of OPDIVO as a single agent are presented in Table 1. (See Table 1) (…) **6 ADVERSE REACTIONS** **MSI-H or dMMR Metastatic Colorectal Cancer** The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, openlabel study. (See Tables 22 and 23) (…) **8 USE IN SPECIFIC POPULATIONS** **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 (12.3), and Clinical Studies (14)]. 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. **14 CLINICAL STUDIES** **14.9 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. (…) (…) Patients enrolled in the single agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg IV every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg IV as a single agent every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression. (…) (…) A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were White. (…) (…) A total of 119 patients were enrolled in the OPDIVO plus ipilimumab MSI-H mCRC cohort. (See Table 36) (…)
018013, 04/09/2019	**Nortriptyline**	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Drugs Metabolized by P450 2D6* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 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). (…)

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Last Updated: 06/2019

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209531, 10/10/2018	Nusinersen	Neurology	SMN2	Clinical Pharmacology, Clinical Studies	**12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants. **14 CLINICAL STUDIES** **14.1 Infantile-Onset SMA** (…) Baseline demographics were balanced between the SPINRAZA and control groups with the exception of age at first treatment (median age 175 vs. 206 days, respectively). The SPINRAZA and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number. (…) **14.3 Presymptomatic SMA** (…) Some patients receiving SPINRAZA before the onset of SMA symptoms survived without requiring permanent ventilation beyond what would be expected based on their SMN2 copy number, and some patients also achieved age-appropriate growth and developmental motor milestones such as the ability to sit unassisted, stand, or walk.
125486, 11/16/2017	Obinutuzumab	Oncology	MS4A1 (CD20 antigen)	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Chronic Lymphocytic Leukemia** GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (Study 1) in 781 patients with previously untreated CD20+ chronic lymphocytic leukemia requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) < 70 mL/min. (…)
208558, 12/19/2018	Olaparib (1)	Oncology	BRCA	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer** Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinumbased chemotherapy. Select patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. **1.3 Advanced gBRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy** Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. [see Dosage and Administration (2.1)]. **1.4 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer** Lynparza is indicated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Information on FDA-approved tests for the detection of BRCA-mutations is available at http://www.fda.gov/companiondiagnostics. *First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian* Cancer Select patients with advanced ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy for maintenance treatment with Lynparza based on the presence of deleterious or suspected deleterious gBRCAm or sBRCAm [see Indications and Usage (1.1) and Clinical Studies (14.2)]. An FDA-approved test for the detection of tumor BRCA gene mutation for the first-line maintenance treatment of advanced ovarian cancer is not currently available. *Advanced gBRCAm Ovarian Cancer* Select patients with advanced ovarian cancer with Lynparza based on the presence of deleterious or suspected deleterious gBRCA-mutation [see Indications and Usage (1.3) and Clinical Studies (14.2)]. *gBRCAm HER2-negative Metastatic Breast Cancer* Select patients for the treatment of HER2-negative metastatic breast cancer with Lynparza based on the presence of deleterious or suspected deleterious gBRCA-mutation [see Indications and Usage (1.4) and Clinical Studies (14.3)]. **2.2 Recommended Dosing** *First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer* Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years. *Advanced gBRCA-mutated Ovarian Cancer* Continue treatment until disease progression or unacceptable toxicity. *Germline BRCA-mutated HER2-negative Metastatic Breast Cancer* Continue treatment until disease progression or unacceptable toxicity. **5 WARNINGS AND PRECAUTIONS** **5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia**

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

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					Overall, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) in patients treated with Lynparza monotherapy in clinical trials, including long-term follow up, was <1.5% % (26/2258) and the majority of events had a fatal outcome. Of these, 22/26 patients had a documented BRCA mutation, 2 patients had gBRCA wildtype and in 2 patients the BRCA mutation status was unknown. (…) **6 ADVERSE REACTIONS** **First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer** *SOLO-1* The safety of Lynparza for the maintenance treatment of patients with BRCA-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1, a placebo-controlled, double-blind study in which 390 patients received either Lynparza 300 mg BID (n=260) or placebo tablets (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo. (…) **Maintenance Treatment of Recurrent Ovarian Cancer** *SOLO-2* The safety of Lynparza for the maintenance treatment of patients with platinum sensitive gBRCAm ovarian cancer was investigated in SOLO-2. This study was a placebo-controlled, double-blind study in which 294 patients received either Lynparza 300 mg (2 x 150 mg tablets) twice daily (n=195) or placebo tablets twice daily (n=99) until disease progression or unacceptable toxicity. (…) **Treatment of Advanced gBRCAm Ovarian Cancer After 3 or More Lines of Chemotherapy** *Pooled data* Treatment with Lynparza (capsule formulation) as monotherapy was studied in 223 patients (pooled from 6 studies) with gBRCAm advanced ovarian cancer who had received 3 or more prior lines of chemotherapy. (…) **Treatment of gBRCAm HER2-negative Metastatic Breast Cancer** *OlympiAD* The safety of Lynparza tablets as monotherapy was also evaluated in gBRCAm patients with HER2- negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD. (…) **14 CLINICAL STUDIES** **14.1 First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer** *SOLO-1* SOLO-1 (NCT01844986) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza with placebo in patients with BRCA-mutated (BRCAm) advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy in which 391 patients were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily (n=260) or placebo (n=131). (…) (…) The median age of patients treated with Lynparza was 53 years (range: 29 to 82) and 53 years (range: 31 to 84) among patients on placebo. The ECOG performance score was 0 in 77% of patients receiving Lynparza and 80% of patients receiving placebo. Of all patients, 82% were White, 36% were enrolled in the U.S. or Canada, and 82% were in complete response to their most recent platinum-based regimen. The majority of patients (n=389) had germline BRCA mutation (gBRCAm), and 2 patients had somatic BRCAm (sBRCAm). Of the 391 patients randomized in SOLO-1, 386 were retrospectively or prospectively tested with BRACAnalysis Test and 383 patients were confirmed to have deleterious or suspected deleterious gBRCAm status; 253 were randomized to the Lynparza arm and 130 to the placebo arm. Two out of 391 patients randomized in SOLO-1 were confirmed to have sBRCAm only based on an investigational tissue assay. (…) **14.2 Maintenance Treatment of Recurrent Ovarian Cancer** The efficacy of Lynparza was investigated in two randomized, placebo-controlled, double-blind, multicenter studies in patients with recurrent ovarian cancers who were in response to platinum-based therapy. *SOLO-2* SOLO-2 (NCT01874353) was a double-blind, placebo-controlled trial in which patients (n=295) with gBRCAm ovarian, fallopian tube, or primary peritoneal cancer were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. (…) All patients had a deleterious or suspected deleterious germline BRCA-mutation as detected either by a local test (n=236) or central Myriad CLIA test (n=59), subsequently confirmed by BRACAnalysis CDx® (n=286). (…) *Study 19* (…) A retrospective analysis for germline BRCA mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious gBRCA mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo. (…) **14.3 Advanced gBRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy** The efficacy of Lynparza was also investigated in a single-arm study of patients with deleterious or suspected deleterious gBRCAm advanced cancers. A total of 137 patients with measurable, advanced gBRCAm ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules at a dose of 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST, version 1.0. The median age of the patients was 58 years, the majority were White (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious gBRCAm status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the BRACAnalysis CDxTM. Efficacy results are summarized in Table 14. (See Table 14) **14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer** *OlympiAD*

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					OlympiAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2- negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. (…) (…) No prior treatment with a PARP inhibitor was permitted. Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx ™ and 297 were confirmed to have deleterious or suspected deleterious gBRCAm status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm. (…)
208558, 12/19/2018	Olaparib (2)	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.4 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer** Lynparza is indicated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** *gBRCAm HER2-negative Metastatic Breast Cancer* Select patients for the treatment of HER2-negative metastatic breast cancer with Lynparza based on the presence of deleterious or suspected deleterious gBRCA-mutation [see Indications and Usage (1.4) and Clinical Studies (14.3)]. **2.2 Recommended Dosing** *Germline BRCA-mutated HER2-negative Metastatic Breast Cancer* Continue treatment until disease progression or unacceptable toxicity. **6 ADVERSE REACTIONS** **Treatment of gBRCAm HER2-negative Metastatic Breast Cancer** OlympiAD The safety of Lynparza tablets as monotherapy was also evaluated in gBRCAm patients with HER2- negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD. (…) **14 CLINICAL STUDIES** **14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer** OlympiAD OlympiAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2- negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. (…)
208558, 12/19/2018	Olaparib (3)	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.4 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer** Lynparza is indicated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1)]. **14 CLINICAL STUDIES** **14.4 Treatment of gBRCAm HER2-negative Metastatic Breast Cancer** OlympiAD OlympiAD (NCT02000622) was an open-label study in which patients (n=302) with gBRCAm HER2- negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. (…) (…) Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors and the proportions were balanced across treatment arms. (…)
761038, 10/19/2016	Olaratumab	Oncology	PDGFRA	Clinical Studies	**14 CLINICAL STUDIES**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					The efficacy of LARTRUVO was demonstrated in Trial 1, an open-label, randomized, active-controlled study. Eligible patients were required to have soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy, a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate but had not been administered, ECOG PS of 0-2, and tumor specimen available for assessment of PDGFR-α expression by an investigational use assay. Patients were randomized (1:1) to receive LARTRUVO in combination with doxorubicin or doxorubicin as a single agent. PDGFR-α expression (positive versus negative), number of previous lines of treatment (0 versus 1 or more), histological tumor type (leiomyosarcoma versus synovial sarcoma versus all others), and ECOG PS (0 or 1 versus 2) were used to allocate patients in the randomization. (…)
203585, 06/21/2017	**Omacetaxine**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Clinical Studies	**14 CLINICAL STUDIES** The efficacy of SYNRIBO was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+]) (whether lost or never achieved); or no major cytogenetic response (MCyR) by 52 weeks (i.e., ≥35% Ph+) (whether lost or never achieved); or progressive leukocytosis. (See Table 5)
207931, 07/23/2018	**Ombitasvir, Paritaprevir, and Ritonavir**	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Clinical Trial Results in Adults with Chronic GT4 HCV Infection without Cirrhosis** (…) HCV GT4-infected subjects had a median age of 51 years (range: 19 to 70); 64% were treatment-naïve, 17% were prior pegIFN/RBV null responders; 7% were prior pegIFN/RBV partial responders, 13% were prior pegIFN/RBV relapsers; 65% were male; 9% were Black; 14% had a body mass index at least 30 kg/m2 ; 70% had baseline HCV RNA levels at least 800,000 IU/mL; 79% had IL28B (rs12979860) non-CC genotype; 7% had bridging fibrosis (F3). (…) **14.3 Clinical Trial Results in Adults with Chronic GT4 HCV Infection with Compensated Cirrhosis** **(…)** Of the 59 subjects in the 12 week arm, median age was 56 years (range: 43 to 81); 51% were treatment-naïve, 29% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 12% were prior pegIFN/RBV relapsers; 76% were male; 17% were Black; 29% had a body mass index of at least 30 kg/m2 ; 76% had baseline HCV RNA levels of at least 800,000 IU per mL; 86% had IL28B (rs12979860) non-CC genotype; 12% had platelet counts of less than 90 x 109 per L; and 5% had albumin less than 3.5 mg per dL. (…)
022056, 08/21/2018	**Omeprazole**	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** *Tacrolimus* Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3) **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are extensive metabolizers and those carrying two loss-of-function alleles are poor metabolizers. In extensive metabolizers, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > extensive metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers. In a pharmacokinetic study of single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four-fold of that in Caucasians [see Dosage and Administration (2.1), Use in Specific Populations (8.7)].
020007, 03/08/2017	**Ondansetron**	Gastroenterology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* (…) 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. (…)

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

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208065, 08/28/2018	Osimertinib	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)** TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)]. **1.2 Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC** TAGRISSO is indicated for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens [see Clinical Studies (14)]. Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TAGRISSO following progression on or after EGFR TKI therapy based on the presence of an EGFR T790M mutation in tumor or plasma specimens [see Clinical Studies (14)]. Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) [see Warnings and Precautions (5)]. The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies. Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. (…) Previously Treated EGFR T790M Mutation-Positive Metastatic Non-Small Cell Lung Cancer The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGFR T790M mutationpositive NSCLC who had progressive disease following first line EGFR TKI treatment. (…) *AURA3 Trial* **14 CLINICAL STUDIES** **14.1 Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer** The efficacy of TAGRISSO was demonstrated in a randomized, multicenter, double-blind, activecontrolled trial (FLAURA [NCT02296125]) in patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, metastatic NSCLC, who had not received previous systemic treatment for metastatic disease. Patients were required to have measurable disease per RECIST v1.1, a WHO performance status of 0-1, and EGFR exon 19 deletion or exon 21 L858R mutation in tumor prospectively identified by the cobas® EGFR Mutation Test in a central laboratory or by an investigational assay at a CLIA-certified or accredited laboratory. (…) (…) Randomization was stratified by EGFR mutation type (exon 19 deletion or exon 21 L858R mutation) and ethnicity (Asian or non-Asian). Patients randomized to the control arm were offered TAGRISSO at the time of disease progression if tumor samples tested positive for the EGFR T790M mutation. (…) (…) With regard to EGFR tumor testing, 63% were exon 19 deletion and 37% were exon 21 L858R; 5 patients (<1%) also had a concomitant de novo T790M mutation. EGFR mutation status was confirmed centrally using the cobas EGFR Mutation Test in 90% of patients. (see Table 6 and Figure 1) (…) **14.2 Previously Treated EGFR T790M Mutation-Positive Metastatic Non-Small Cell Lung Cancer** The efficacy of TAGRISSO was demonstrated in a randomized, multicenter open-label, active-controlled trial in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI (AURA3). All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas® EGFR Mutation Test performed in a central laboratory prior to randomization. (…)

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

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203505, 01/25/2019	**Ospemifene (1)**	Gynecology	CYP2C9	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** **Drug Interactions** *Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug* Warfarin Ospemifene 60 mg was given after a light breakfast (two slices of bread with ham and cheese and juice) once daily for 12 days in sixteen postmenopausal women who were determined to be rapid metabolizers of CYP2C9 (CYP2C9*1/*1 or CYP2C9*1/*2). On Day 8, a single dose of warfarin 10 mg and vitamin K 10 mg were administered one hour after a light breakfast. The geometric mean ratio (90% CI) for S-warfarin with and without ospemifene for Cmax and AUC0-inf were 0.97 (0.92-1.02) and 0.96 (0.91-1.02), respectively. Multiple doses of ospemifene did not significantly affect the pharmacokinetics of a single dose of warfarin. No study was conducted with multiple doses of warfarin.
203505, 01/25/2019	**Ospemifene (2)**	Gynecology	CYP2B6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** **Drug Interactions** *Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug* Bupropion Ospemifene 60 mg was administered once daily for seven consecutive days after the evening meal in sixteen postmenopausal women (not homozygous for CYP2B6*6). On the Day 8 after overnight fast, a single 150 mg dose of sustained release bupropion was administered in morning under fasted condition. The geometric mean ratio (90% CI) for bupropion with and without ospemifene for Cmax and AUC0-inf were 0.82 (0.75-0.91) and 0.81 (0.77-0.86), respectively. The geometric mean ratio (90% CI) for hydroxybupropion, an active metabolite formed via CYP2B6, with and without ospemifene for Cmax and AUC0-inf were 1.16 (1.09-1.24) and 0.98 (0.92-1.04), respectively.
202810, 12/13/2018	**Oxcarbazepine**	Neurology	HLA-B	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.4 Serious Dermatological Reactions** *Association with HLA-B*1502* Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN with Oxtellar XR treatment. Human Leukocyte Antigen (HLA) allele B*1502 increases the risk for developing SJS/TEN in patients treated with carbamazepine. The chemical structures of immediate release oxcarbazepine and Oxtellar XR are similar to that of carbamazepine. Available clinical evidence, and data from nonclinical studies showing a direct interaction between immediate release oxcarbazepine and HLA-B*1502 protein, suggest that the HLAB*1502 allele may also increase the risk for SJS/TEN with Oxtellar XR. The frequency of HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations, is about 8% in Thai populations, and above 15% in the Philippines and in some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in people from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations, and in Japanese (<1%). Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Oxtellar XR. The use of Oxtellar XR should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Consideration should also be given to avoid the use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low, or in current Oxtellar XR users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status. The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been well characterized.
208032, 11/02/2018	**Oxymetazoline and Tetracaine (1)**	Anesthesiology	G6PD	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
208032, 11/02/2018	**Oxymetazoline and Tetracaine (2)**	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.1 Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure,and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue KOVANAZE and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.
207103, 04/04/2019	**Palbociclib (1)**	Oncology	ESR (Hormone Receptor)	Indications and Usage, Adverse	**1 INDICATIONS AND USAGE**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Reactions, Clinical Studies	IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: • an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or • fulvestrant in patients with disease progression following endocrine therapy. **6 ADVERSE REACTIONS** **6.1 Clinical Studies Experience** **Study 1: IBRANCE plus Letrozole** **Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy** The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months. (…) **Study 2: IBRANCE plus Fulvestrant** **Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy** The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months. (…) **Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer** Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE. **14 CLINICAL STUDIES** **Study 1: IBRANCE plus Letrozole** **Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy** Study 1 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. (…) **Study 2: IBRANCE plus Fulvestrant** **Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy** Study 2 (PALOMA-3) was an international, randomized, double-blind, parallel group, multicenter study of IBRANCE plus fulvestrant versus placebo plus fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…)
207103, 04/04/2019	**Palbociclib (2)**	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: • an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or • fulvestrant in patients with disease progression following endocrine therapy. **6 ADVERSE REACTIONS** **6.1 Clinical Studies Experience** **Study 1: IBRANCE plus Letrozole** **Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy** The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months. (…) **Study 2: IBRANCE plus Fulvestrant** **Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy** The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months. (…) **Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer** Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					14 CLINICAL STUDIES **Study 1: IBRANCE plus Letrozole** **Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy** Study 1 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. (…) **Study 2: IBRANCE plus Fulvestrant** **Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy** Study 2 (PALOMA-3) was an international, randomized, double-blind, parallel group, multicenter study of IBRANCE plus fulvestrant versus placebo plus fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. (…)
021999, 01/25/2019	**Paliperidone**	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and Elimination* (…) Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. (…)
021372, 09/18/2014	**Palonosetron**	Gastroenterology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-Shydroxy-palonosetron. These metabolites each have less than 1% of the 5- HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.
125147, 06/29/2017	**Panitumumab (1)**	Oncology	EGFR	Adverse Reactions, Clinical Pharmacology, Clinical Studies	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) Safety data are presented from two clinical trials in which patients received Vectibix: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 20050203 are limited to 656 patients with wild-type KRAS mCRC. The safety profile of Vectibix in patients with wild-type RAS mCRC is similar with that seen in patients with wild-type KRAS mCRC. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** (…) A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age (21-88 years), gender, race (15% nonwhite), mild-tomoderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, and 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab. No formal pharmacokinetic studies of panitumumab have been conducted in patients with renal or hepatic impairment. **14 CLINICAL STUDIES** **14.1 Recurrent or Refractory mCRC** The safety and efficacy of Vectibix was demonstrated in Study 20020408, an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum, in Study 20080763, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type KRAS mCRC, and in Study 20100007, an open-label, multicenter, multinational, randomized trial of 377 patients with wild-type KRAS mCRC. (…)
125147, 06/29/2017	**Panitumumab (2)**	Oncology	RAS	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Metastatic Colorectal Cancer** Vectibix is indicated for the treatment of patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) [see Dosage and Administration (2.1)]: • As first-line therapy in combination with FOLFOX [see Clinical Studies (14.2)]. • As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy [see Clinical Studies (14.1)]. Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown [see Dosage and Administration (2.1), Warnings and Precautions (5.2), and Clinical Pharmacology (12.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection**

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Last Updated: 06/2019

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					Prior to initiation of treatment with Vectibix, assess RAS mutational status in colorectal tumors and confirm the absence of a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of both KRAS and NRAS. Information on FDA-approved tests for the detection of RAS mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/CompanionDiagnostics. **5 WARNINGS AND PRECAUTIONS** **5.2 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with RAS-Mutant mCRC** Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereafter is referred to as "RAS" [see Indications and Usage (1.1), Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14)]. Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of RAS mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing RAS mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents [see Indications and Usage (1.1), and Clinical Pharmacology (12.1)]. Additionally, in Study 20050203, 272 patients with RAS-mutant mCRC tumors received Vectibix in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with RAS-mutant mCRC who received Vectibix and FOLFOX versus FOLFOX alone [see Indications and Usage (1.1)]. **6 ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the label: • (…) Increased Tumor Progression, Increased Mortality, or Lack of Benefit in RAS-Mutant mCRC [see Indications and Usage (1.1) and Warnings and Precautions (5.2)] (…) **6.1 Clinical Trials Experience** (…) 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 FOLFOX Chemotherapy* The most commonly reported adverse reactions (≥ 20%) in patients with wild-type KRAS mCRC receiving Vectibix (6 mg/kg every 2 weeks) and FOLFOX therapy (N = 322) in Study 20050203 were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin (Table 2). Serious adverse reactions (≥ 2% difference between treatment arms) in Vectibix-treated patients with wildtype KRAS mCRC were diarrhea and dehydration. The commonly reported adverse reactions (≥ 1%) leading to discontinuation in patients with wild-type KRAS mCRC receiving Vectibix were rash, paresthesia, fatigue, diarrhea, acneiform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypokalemia, occurred in a patient who received Vectibix. (See Table 2) (…) **14 CLINICAL STUDIES** **14.1 Recurrent or Refractory mCRC** The safety and efficacy of Vectibix was demonstrated in Study 20020408, an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum, and in Study 20080763, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type KRAS mCRC, and in Study 20100007, an open-label, multicenter, multinational, randomized trial of 377 patients with wild-type KRAS mCRC. (…) *Study 20020408 (NCT00113763)* (…) The study results were analyzed in the wild-type KRAS subgroup where KRAS status was retrospectively determined using archived paraffin-embedded tumor tissue. KRAS 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 20080763was an open-label, multicenter, multinational, randomized (1:1) clinical trial, stratified by region (North America, Western Europe, and Australia versus rest of the world) and ECOG PS (0 and 1 vs 2) in patients with wild-type KRAS mCRC. (See Table 3 and Figure 1) (…) *Study 20100007 (NCT01412957)* *Study 20100007 was an open-label, multicenter, randomized (1:1) clinical study stratified by ECOG performance status (0 or 1 vs 2) and region (sites in Europe versus Asia versus rest of world) in patients with wild-type KRAS mCRC. Eligible patients were required to have received prior therapy with irinotecan, oxaliplatin, and a thymidylate synthase inhibitor, and have wild-type KRAS exon 2 mCRC as determined by a clinical trial assay. An assessment for RAS status (defined as KRAS exons 2, 3, and 4 and NRAS exons 2, 3, and 4) using Sanger sequencing was conducted in patients for whom tumor tissue was available. Patients were randomized to receive Vectibix (6 mg/kg intravenously every 14 days) plus BSC or BSC alone. Patients received Vectibix and BSC or BSC until disease progression, withdrawal of consent, unacceptable toxicity, or death. Patients randomized to BSC were not offered Vectibix at the time of disease progression. The major efficacy outcome measure was OS in patients with wild-type KRAS mCRC. Secondary efficacy outcome measures included OS in the subgroup of patients with wild-type RAS mCRC; PFS and ORR in patients with wild-type KRAS; and PFS and ORR in the subgroup of patients with wild-type RAS mCRC.* (…)

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Last Updated: 06/2019

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					(…) KRAS tumor mutation status was available for all patients and RAS tumor mutation status was available for 86% of the 377 patients. Among the 377 patients, 270 (72%) patients had wild-type RAS tumors, 54 (14%) had mutant RAS tumors, and 54 (14%) had unknown RAS tumor status. (See Table 4 and Figure 2). **14.2 First-line in Combination with FOLFOX Chemotherapy** (…) The prespecified major efficacy measure was PFS in patients (n = 656) with wild-type KRAS mCRC as assessed by a blinded independent central review of imaging. Other key efficacy measures included OS and ORR. In Study 20050203, in the wild-type KRAS subgroup (n = 656), 64% of patients were men, 92% White, 2% Black, and 4% Hispanic or Latino. Sixty-six percent of patients had colon cancer and 34% had rectal cancer. ECOG performance was 0 in 56% of patients, 1 in 38% of patients, and 2 in 6% of patients. Median age was 61.5 years. The efficacy results in Study 20050203 in patients with wild-type KRAS mCRC are presented in Table 5 below. (See Table 5) (…) *(…)* *Exploratory Analysis of OS* An exploratory analysis of OS with updated information based on events in 82% of patients with wild-type KRAS mCRC estimated the treatment effect of Vectibix plus FOLFOX compared with FOLFOX alone on OS (Figure 3). Median OS among 325 patients with wild-type KRAS mCRC who received Vectibix plus FOLFOX was 23.8 months (95% CI: 20.0, 27.7) vs 19.4 months (95% CI: 17.4, 22.6) among 331 patients who received FOLFOX alone (HR = 0.83, 95% CI: 0.70, 0.98). (See Figure 3) *Retrospective exploratory analyses in the RAS wild-type subgroup* Among the 656 patients with wild-type KRAS exon 2 mCRC, RAS mutation status was assessed for 620 patients using Sanger bidirectional sequencing and Surveyor®/WAVE® analysis. Of these 620 patients, approximately 17% of patients (n = 104) tumors harbored mutations in KRAS exons 3 or 4 or in NRAS exons 2, 3, and 4. Retrospective subset analyses were then conducted among the subset of patients without RAS mutations (n = 512) as described above. In the wild-type RAS subgroup, 65% of patients were men and 91% were White, 2% Black, and 5% Hispanic or Latino. Sixty-five percent of patients had colon cancer and 35% had rectal cancer. ECOG performance was 0 in 57% of patients, 1 in 37% of patients, and 2 in 6% of patients. Median age was 61 years. (See Table 6 and Figure 4) **14.3 RAS-Mutant mCRC** Vectibix is not effective for the treatment of patients with RAS-mutant mCRC, defined as a RAS mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), or exon 4 (codons 117 and 146) of KRAS and NRAS. In Study 20050203, among patients with RAS-mutant tumors, the median PFS was 7.3 months (95% CI: 6.3, 7.9) among 272 patients receiving Vectibix plus FOLFOX and 8.7 months (95% CI: 7.6, 9.4) among patients who received FOLFOX alone (HR = 1.31, 95% CI: 1.07, 1.60). The median OS was 15.6 months (95% CI: 13.4, 17.9) among patients receiving Vectibix plus FOLFOX and 19.2 months (95% CI: 16.7, 21.8) among patients who received FOLFOX alone (HR = 1.25, 95% CI: 1.02, 1.55). In Study 20100007, among patients with RAS-mutant tumors, no differences in OS or PFS were observed between the treatment arms [n = 54; OS HR = 0.99 (95% CI: 0.49, 2.00); PFS HR = 1.03 (95% CI: 0.56, 1.90)].
020987, 04/25/2019	**Pantoprazole**	Gastroenterology	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Patients with Hepatic Impairment* In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Doses higher than 40 mg/day have not been studied in hepatically impaired patients. **12.5 Pharmacogenomics** CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10 hours in adults, they still have minimal accumulation (23% or less) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed. Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10 fold lower apparent oral clearance compared to extensive metabolizers. For known pediatric poor metabolizers, a dose reduction should be considered.
125511, 12/17/2018	**Parathyroid Hormone**	Inborn Errors of Metabolism	CASR	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. *Limitations of Use:* • Because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone [see Warnings and Precautions (5.1)]. • NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations. • NATPARA was not studied in patients with acute post-surgical hypoparathyroidism. **14 CLINICAL STUDIES** *Study in Patients with Established Hypoparathyroidism* (…) Patients with hypoparathyroidism due to calcium-sensing receptor mutations were excluded from the trial. (…)

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

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021299, 01/04/2017	Paroxetine	Psychiatry	CYP2D6	Drug Interactions	**DRUG INTERACTIONS** (…) In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine Cmax values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine. (…)
210922, 08/10/2018	Patisiran	Neurology	TTR	Adverse Reactions, Clinical Pharmacology, Clinical Studies	**6 ADVERSE REACTIONS** (…) At baseline, 46% of patients were in Stage 1 of the disease and 53% were in Stage 2. Forty-three percent of patients had Val30Met mutations in the transthyretin gene; the remaining patients had 38 other point mutations. Sixty-two percent of ONPATTRO-treated patients had non-Val30Met mutations, compared to 48% of the placebo-treated patients. (…) **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** (…) Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race. (…) **14 CLINICAL STUDIES** (…) Patients receiving ONPATTRO experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, Val30Met mutation status, and disease stage.
022465, 05/31/2017	Pazopanib (1)	Oncology	UGT1A1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Pazopanib can increase serum total bilirubin levels [see Warnings and Precautions (5.1)]. In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. A pooled pharmacogenetic analysis of 236 Caucasian patients evaluated the TA-repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during pazopanib treatment. In this analysis, the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic susceptibility to Gilbert's syndrome) was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes.
022465, 05/31/2017	Pazopanib (2)	Oncology	HLA-B	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** (…) In a pooled pharmacogenetic analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, ALT > 3 X ULN (NCI CTC Grade 2) occurred in 32% (42/133) of HLA-B*57:01 allele carriers and in 19% (397/2101) of non-carriers and ALT > 5 X ULN (NCI CTC Grade 3) occurred in 19% (25/133) of HLA-B*57:01 allele carriers and in 10% (213/2101) of non-carriers. In this dataset, 6% (133/2234) of the patients carried the HLA-B*57:01 allele. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype [see Warnings and Precautions (5.1)].
103949, 01/08/2019	Peginterferon Alfa-2b	Infectious Diseases	IFNL3 (IL28B)	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** A retrospective genome-wide association analysis1,2 of 1671 subjects (1604 subjects from Study 4 [see Clinical Studies (14.1)] and 67 subjects from another clinical trial) was performed to identify human genetic contributions to anti-HCV treatment response in previously untreated HCV genotype 1 subjects. A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (IL28B rs12979860) was associated with variable SVR rates. The rs12979860 genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1587), SVR rates by rs12979860 genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to IL28B genotype was consistent across various racial/ethnic groups (see Table 14). Other variants near the IL28B gene (e.g., rs8099917 and rs8103142) have been identified; however, they have not been shown to independently influence SVR rates during treatment with pegylated interferon alpha therapies combined with ribavirin. (See Table 13)
125293, 07/13/2018	Pegloticase	Rheumatology	G6PD	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information	**BOXED WARNING** WARNING: ANAPHYLAXIS and INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA (…) Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency (4, 5.3). **4 CONTRAINDICATIONS** Glucose-6-phosphate dehydrogenase (G6PD) deficiency [See Warnings and Precautions (5.3)] **5 WARNINGS AND PRECAUTIONS** **5.3 G6PD Deficiency Associated Hemolysis and Methemoglobinemia** 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. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency. **17 PATIENT COUNSELING INFORMATION** *Glucose-6-phosphate dehydrogenase (G6PD) Deficiency*

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Last Updated: 06/2019

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					Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known. [See Warnings and Precautions (5.3), Contraindications (4)]
125514, 06/17/2019	**Pembrolizumab (1)**	Oncology	BRAF	Adverse Reactions, Clinical Studies	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Ipilimumab-Refractory Melanoma* The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. (…) **14 CLINICAL STUDIES** **14.1 Melanoma** *Ipilimumab-Naive Melanoma* (…) Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. (…) (…) A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease, 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. (…) *Ipilimumab-Refractory Melanoma* (…) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. (…) (…) Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease. (…) *Melanoma* *Ipilimumab-Refractory Melanoma* (…) Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. (…) (…) The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator's choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 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. (…) *Adjuvant Treatment of Resected Melanoma* (…) The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IUO assay. (…)
125514, 06/17/2019	**Pembrolizumab (2)**	Oncology	CD274 (PD-L1)	Indications and Usage, Dosage and Administration, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 Non-Small Cell Lung Cancer** KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC. KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations, and is: • stage III where patients are not candidates for surgical resection or definitive chemoradiation, or • metastatic. KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. **1.4 Head and Neck Squamous Cell Cancer** KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC). KEYTRUDA, as a single agent, is indicated for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test [see Dosage and Administration (2.1)].

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. **1.7 Urothelial Carcinoma** KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test [see Dosage and Administration (2.1)], or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14.7)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. **1.9 Gastric Cancer** KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy [see Clinical Studies (14.7)]. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. **1.10 Cervical Cancer** KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14.10)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, or Cervical Cancer** Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in: • stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation [see Clinical Studies (14.2)]. • metastatic NSCLC [see Clinical Studies (14.2)]. • first-line treatment of metastatic or unresectable, recurrent HNSCC [see Clinical Studies (14.4)]. • metastatic urothelial carcinoma [see Clinical Studies (14.7)]. • metastatic gastric cancer [see Clinical Studies (14.9)]. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing. • recurrent or metastatic cervical cancer [see Clinical Studies (14.10)]. Information on FDA-approved tests for the detection of PD-L1 expression for these indications is available at: http://www.fda.gov/CompanionDiagnostics. **14 CLINICAL STUDIES** **14.1 Melanoma** *Ipilimumab-Naive Melanoma* (…) Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. (…) (…) A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor. (…) *Adjuvant Treatment of Resected Melanoma* (…) The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually. The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IUO assay. (…) For patients with PD-L1 positive tumors, the HR was 0.54 (95% CI: 0.42, 0.69); p<0.001. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression. **14.2 Non-Small Cell Lung Cancer** *First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy* The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, activecontrolled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). (…) (…) The study population characteristics were: median age of 64 years (range: 34 to 84); 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG performance status of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% [negative]. (See Table 21) (…) *First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nabpaclitaxel chemotherapy* The efficacy of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PDL1 status (TPS<1% [negative] vs. TPS ≥1%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). (…) (…) The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; 71% ECOG performance status of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS<1%; 19% were from the East Asian region; and 60% received paclitaxel. (…) *First-line treatment of metastatic NSCLC as a single agent* The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. (…) (…) Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥50% vs. TPS 1 to 49%). (…) (…) The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 32 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%. (See Table 32) (…) The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≥50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11). (See Figure 6) (…) *KEYNOTE-024* The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were eligible. (…) *Previously treated NSCLC* The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG performance scale (0 vs. 1), and geographic region (East Asia vs. non-East Asia). (…) (…)The study population characteristics were: median age 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG performance status 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinumdoublet regimen, 29% received two or more prior therapies for their metastatic disease. (…) **14.4 Head and Neck Squamous Cell Cancer** *First-line treatment of metastatic or unresectable, recurrent HNSCC* The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). (…) (…) A retrospective re-classification of patients' tumor PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx kit was conducted using the tumor specimens used for randomization. (…) (…) The study population characteristics were: median age of 61 years (range: 20 to 94), 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20. (…) The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. The trial also demonstrated a

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. (…) In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI:0.51, 0.94). **14.7 Urothelial Carcinoma** Cisplatin Ineligible Patients with Urothelial Carcinoma (…) Among the 370 patients, 30% (n = 110) had tumors that expressed PD-L1 with a combined positive score (CPS) of ≥ 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The study population characteristics of these 110 patients were: median age 73 years, 68% male, and 87% White. (See Table 41) (…) Previously Untreated Urothelial Carcinoma KEYNOTE-361 (NCT02853305) is an ongoing, multicenter, randomized study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study compares KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. The trial also enrolled a third arm of monotherapy with KEYTRUDA to compare to platinum-based chemotherapy alone. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that in patients classified as having low PD-L1 expression (CPS <10), those treated with KEYTRUDA monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended to stop further accrual of patients with low PD-L1 expression in the monotherapy arm, however, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm. **14.8 Microsatellite Instability-High Cancer** See Table 30 **14.9 Gastric Cancer** (…) Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. (…) **14.10 Cervical Cancer** (…) Among the 98 patients in Cohort E, 77 (79%) had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy in the metastatic setting. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. (…) (…) No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 33 for patients with PD-L1 expression (CPS ≥1). (See Table 48) (…) **14.13 Renal Cell Carcinoma** The efficacy of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease requiring systemic immunosuppression within the last 2 years were ineligible. (…) **(…)** Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status. (…)
125514, 06/17/2019	**Pembrolizumab (3)**	Oncology	Microsatellite Instability, Mismatch Repair	Indications and Usage, Dosage and Administration, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** **1.8 Microsatellite Instability-High Cancer** KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient • solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.6)]. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. **2 DOSAGE AND ADMINISTRATION** **2.9 Recommended Dosage for MSI-H Cancer** The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression [see Clinical Studies (14.6)]. The recommended dose of KEYTRUDA in children is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. **8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** The safety and effectiveness of KEYTRUDA have been established in pediatric patients with cHL, PMBCL, and MSI-H cancer. Use of KEYTRUDA in pediatric patients with cHL, PMBCL, and MSI-H cancers is supported by evidence from adequate and well-controlled studies of KEYTRUDA in adults with additional pharmacokinetic and safety data in pediatric patients [see Adverse Reactions (6.1), Clinical Studies (14,4, 14.5, 14.7), Clinical Pharmacology (12.3)]. **14 CLINICAL STUDIES** **14.8 Microsatellite Instability-High Cancer** The efficacy of KEYTRUDA was evaluated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. (…) (See Table 43)

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

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					A total of 149 patients with MSI-H or dMMR cancers were identified across the five clinical trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy. 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 Table 44) **14.9 Gastric Cancer** (…) Among the 259 patients enrolled in KEYNOTE-059, 7 (3%) had tumors that were determined to be MSI-H. An objective response was observed in 4 patients, including 1 complete response. The duration of response ranged from 5.3+ to 14.1+ months.
125514, 06/17/2019	**Pembrolizumab (4)**	Oncology	EGFR	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 Non-Small Cell Lung Cancer** KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC. KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations, and is: • stage III where patients are not candidates for surgical resection or definitive chemoradiation, or • metastatic. KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *NSCLC* *First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy* The safety of KEYTRUDA in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.2)]. (…) Previously Untreated NSCLC The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC [see Clinical Studies (14.2)]. Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator's choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. (…) *Previously Treated NSCLC* The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations [see Clinical Studies (14.2)]. **14 CLINICAL STUDIES** **14.2 Non-Small Cell Lung Cancer** First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, activecontrolled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. (…) First-line treatment of metastatic NSCLC as a single agent *KEYNOTE-042* The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. (…) Previously treated NSCLC

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

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					The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. (…) (…) The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinumdoublet regimen, 29% received two or more prior therapies for their metastatic disease. (…)
125514, 06/17/2019	**Pembrolizumab (5)**	Oncology	ALK	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 Non-Small Cell Lung Cancer** KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC. KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with no EGFR or ALK genomic tumor aberrations, and is: • stage III where patients are not candidates for surgical resection or definitive chemoradiation, or • metastatic. KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *NSCLC* *First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy* The safety of KEYTRUDA in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.2)]. (…) Previously Untreated NSCLC The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC [see Clinical Studies (14.2)]. Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator's choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. (…) *Previously Treated NSCLC* The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations [see Clinical Studies (14.2)]. **14 CLINICAL STUDIES** **14.2 Non-Small Cell Lung Cancer** First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, activecontrolled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. (…) First-line treatment of metastatic NSCLC as a single agent *KEYNOTE-042* The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. (…) Previously treated NSCLC The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. (…) (…) The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91%

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinumdoublet regimen, 29% received two or more prior therapies for their metastatic disease. (…)
010775, 05/10/2002	**Perphenazine**	Psychiatry	CYP2D6	Precautions, Clinical Pharmacology	**PRECAUTIONS** *Drug Interactions* Metabolism of a number of medications, including antipsychotics, antidepressants, b- blockers, and antiarrhythmics, occurs through the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called "poor" metabolizers. Among other populations the prevalence is not known. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. In one study of 45 elderly patients suffering from dementia treated with perphenazine, the 5 patients who were prospectively identified as poor P450 2D6 metabolizers had reported significantly greater side effects during the first 10 days of treatment than the 40 extensive metabolizers, following which the groups tended to converge. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** (…) The pharmacokinetics of perphenazine covary with the hydroxylation of debrisoquine which is mediated by cytochrome P450 2D6 (CYP 2D6) and thus is subject to genetic polymorphism- ie, 7%-10% of Caucasians and a low percentage of Asians have little or no activity and are called "poor metabolizers." Poor metabolizers of CYP 2D6 will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or "extensive" metabolizers. (…)
125409, 12/18/2018	**Pertuzumab (1)**	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Metastatic Breast Cancer (MBC)** PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. **1.2 Early Breast Cancer (EBC)** PERJETA is indicated for use in combination with trastuzumab and chemotherapy for • the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer [see Dosage and Administration (2.2) and Clinical Studies (14.2)]. • the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence [see Dosage and Administration (2.2) and Clinical Studies (14.3)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. **5 WARNINGS AND PRECAUTIONS** **5.1 Left Ventricular Dysfunction** Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered [Dosage and Administration (2.3)]. (…) **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Metastatic Breast Cancer (MBC)* (…) The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in Study 1. (…) *Adjuvant Treatment of Breast Cancer (APHINITY)* The adverse reactions described in Table 6 were identified in 4769 patients with HER2-positive early breast cancer treated in APHINITY. (…) **12 CLINICAL PHARMACOLOGY** **12.6 Cardiac Electrophysiology** The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in CLEOPATRA. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design. **14 CLINICAL STUDIES** **14.1 Metastatic Breast Cancer**

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Last Updated: 06/2019

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					CLEOPATRA (NCT00567190) was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2- positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment. (…) (…) 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** *NeoSphere* NeoSphere (NCT00545688) was a multicenter, randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab, or PERJETA plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. *TRYPHAENA* An additional neoadjuvant study (TRYPHAENA, NCT00976989) was conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. (…) *BERENICE* A two-arm non-randomized study (BERENICE, NCT02132949) was conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer. HER2 overexpression was defined as a score of 3+ IHC or ISH amplification ratio of 2.0 or greater as determined by a central laboratory. (…) **14.3 Adjuvant Treatment of Breast Cancer** APHINITY (NCT01358877) was a multicenter, randomized, double-blind, placebo-controlled study conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. (…)
125409, 12/18/2018	**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 positive tumors, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab. (…) (…) Consistent results were observed across several patient subgroups including age (< 65 or 547 ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52). (…) **14.2 Neoadjuvant Treatment of Breast Cancer** *NeoSphere* (…) Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. (…) (…) Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR positive). (…) (…) The pCR rates and magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors. (See Table 8) (…) *TRYPHAENA* (…) The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%, 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI: 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%, 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively. (…) *BERENICE* (…) The pCR (ypT0/is ypN0) rates were 61.8% (95% CI: 54.7, 68.6) and 60.7% (95% CI: 53.6, 67.5) for patients treated with ddAC followed by PERJETA plus trastuzumab and paclitaxel, or FEC followed by PERJETA plus trastuzumab and docetaxel, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 51.6% (95% CI: 42.6, 60.5%) and 57.3% (95% CI: 48.1, 66.1%) than with hormone receptor-negative tumors: 81.5% (95% CI: 70.0, 90.1%) and 68.0% (95% CI: 56.2, 78.3%), respectively. **14.3 Adjuvant Treatment of Breast Cancer**

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Last Updated: 06/2019

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					APHINITY (NCT01358877) was a multicenter, randomized, double-blind, placebo-controlled study conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. Patients were then randomized to receive PERJETA or placebo, in combination with adjuvant trastuzumab and chemotherapy. Randomization was stratified by the following factors: region, nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen. (…) (…) Demographics were generally balanced between the two treatment arms. The median age was 51 years (range 18-86), 13% of patients were 65 or older, and over 99% of patients were female. Sixty-three percent of patients had node-positive disease, 64% had hormone receptor-positive disease, and 71% were Caucasian. All patients had an ECOG performance status of 0 or 1. Seventy-eight percent received an anthracycline containing regimen. (See Tables 9 and 10) (…)
010151, 06/16/2016	**Phenytoin (1)**	Neurology	CYP2C9	Clinical Pharmacology	**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. (…)
010151, 06/16/2016	**Phenytoin (2)**	Neurology	CYP2C19	Clinical Pharmacology	**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. (…)
010151, 06/16/2016	**Phenytoin (3)**	Neurology	HLA-B	Warnings	**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*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502. The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.
017473, 09/27/2011	**Pimozide**	Psychiatry	CYP2D6	Dosage and Administration, Precautions	**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. At doses above 4 mg/day, CYP 2D6 genotyping should be performed. In poor CYP 2D6 metabolizers, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days (see Precautions – Pharmacogenomics). **PRECAUTIONS** *Pharmacogenomics* Individuals with genetic variations resulting in poor CYP 2D6 metabolism (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than extensive CYP 2D6 metabolizers. The concentrations observed in poor CYP 2D6 metabolizers are similar to those seen with strong CYP 2D6 inhibitors such as paroxetine. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP 2D6 metabolizers because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically poor CYP 2D6 metabolizers (see Dosage and Administration).
018147, 05/03/2019	**Piroxicam**	Rheumatology	CYP2C9	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism*

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Last Updated: 06/2019

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					(…) Higher systemic exposure of piroxicam has been noted in subjects with CYP2C9 polymorphisms compared to normal metabolizer type subjects [see Clinical Pharmacology (12.5)]. **12.5 Pharmacogenomics** CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/*2 (n=9), heterozygous CYP2C9*1/*3 (n=9), and homozygous CYP2C9*3/*3 (n=1) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/*1 (n=17, normal metabolizer genotype) following administration of a single oral dose. The mean elimination half-life values of piroxicam for subjects with CYP2C9*1/*3 (n=9) and CYP2C9*3/*3 (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with CYP2C9*1/*1 (n=17). It is estimated that the frequency of the homozygous*3/*3 genotype is 0% to 1% in the population at large; however, frequencies as high as 5.7% have been reported in certain ethnic groups. *Poor Metabolizers of CYP2C9 Substrates* In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance.
203469, 10/18/2018	**Ponatinib**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies	**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 T315Ipositive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). *Limitations of use* Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML [see Warnings and Precautions (5.7)]. **5 WARNINGS AND PRECAUTIONS** **5.2 Venous Thromboembolism** Venous thromboembolic events occurred in 6% (25/449) of Iclusig-treated patients, including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients) with vision loss. In the phase 2 trial, the incidence of venous thromboembolism was 9% (3/32) in patients with Ph+ ALL, 10% (6/62) in patients with blast phase (BP) CML, 4% (3/85) in patients with AP-CML, and 5% (13/270) in patients with CP-CML. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism [see Dosage and Administration (2.3)]. **5.4 Hepatotoxicity** Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts. (…) **5.10 Hemorrhage** Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Iclusig in the phase 2 trial, with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% (4/449 and 4/449, respectively). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia [see Warnings and Precautions (5.13)]. Interrupt Iclusig for serious or severe hemorrhage and evaluate [see Dosage and Administration (2.3)]. **5.13 Myelosuppression** Myelosuppression was reported as an adverse reaction in 59% (266/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Iclusig. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (…) **5.14 Tumor Lysis Syndrome** Two patients (<1%) treated with Iclusig developed serious tumor lysis syndrome. One case occurred in a patient with advanced AP-CML and one case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig. **6 ADVERSE REACTIONS** **6.1 Clinical Trial Experience** *Previously Treated CML or Ph+ ALL* The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. (…) (…) At the time of analysis (48 months of follow-up), 133 patients (30%) were ongoing (110 CP-CML; 20 AP-CML; 3 BPCML; 0 Ph+ ALL), and the median duration of treatment with Iclusig was 32.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML, and 2.7 months in patients with Ph+ ALL. (…) (…) The rates of treatment-emergent adverse reactions resulting in discontinuation were 19% in CP-CML, 12% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse reactions that led to treatment discontinuation was thrombocytopenia (4%). (See Table 5) (…) *Laboratory Abnormalities* (…) Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. (See Table 7) (…)

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					8 USE IN SPECIFIC POPULATIONS **8.5 Geriatric Use** One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (40%) as compared with patients < 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a similar hematologic response rate (45%) as compared with patients < 65 years of age (44%). (…) **14 CLINICAL STUDIES** The safety and efficacy of Iclusig in patients with CML and Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter trial. Efficacy results described below should be interpreted within the context of updated safety information [see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1, 5.2)]. All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML /Philadelphia-positive acute lymphoblastic leukemia [BP-CML/Ph+ ALL]), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation. Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with APCML, BP-CML, or Ph+ ALL. The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). The trial enrolled 449 patients, of which 444 were eligible for efficacy analysis: 267 patients with CP-CML (R/I Cohort: n=203, T315I: n=64), 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ ALL. Five patients were not eligible for efficacy analysis due to lack of confirmation of T315I mutation status, and these patients had not received prior dasatinib or nilotinib. (See Table 11) (…) (…) At the time of analysis, there were 133 patients ongoing (110 patients with CP-CML; 20 patients with AP-CML; 3 patients with BP-CML; 0 patients with Ph+ ALL), and the median duration of Iclusig treatment was 32.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML and 2.7 months in patients with Ph+ ALL. (See Table 12 and 13) (…) (…) The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 0.7 months (range: 0.4 to 5.8 months),1.0 month (range 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months), respectively. The median duration of MaHR for patients with AP-CML, BP-CML, and Ph+ ALL was 12.9 months (range: 1.2 to 52+ months), 6.0 months (range: 1.8 to 47.4+ months), and 3.2 months (range: 1.8 to 12.8+ months), respectively.
022307, 03/28/2019	**Prasugrel (1)**	Cardiology	CYP2C19	Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**8 USE IN SPECIFIC POPULATIONS** **8.9 Metabolic Status** In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **14 CLINICAL STUDIES** (…) There is, however, an alternative explanation: both prasugrel and clopidogrel are 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, 03/28/2019	**Prasugrel (2)**	Cardiology	CYP2C9	Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**8 USE IN SPECIFIC POPULATIONS** **8.9 Metabolic Status** In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **14 CLINICAL STUDIES**

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022307, 03/28/2019	Prasugrel (3)	Cardiology	CYP3A5	Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**8 USE IN SPECIFIC POPULATIONS** **8.9 Metabolic Status** In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **14 CLINICAL STUDIES** (…) There is, however, an alternative explanation: both prasugrel and clopidogrel are 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, 03/28/2019	Prasugrel (4)	Cardiology	CYP2B6	Use in Specific Populations, Clinical Pharmacology, Clinical Studies	**8 USE IN SPECIFIC POPULATIONS** **8.9 Metabolic Status** In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. **14 CLINICAL STUDIES** (…) There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel's active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel's active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. (…)
008316, 06/22/2017	Primaquine (1)	Infectious Diseases	G6PD	Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage	**CONTRAINDICATIONS** Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Warnings). **WARNINGS** *Hemolytic anemia and G6PD deficiency* Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Primaquine should not be prescribed for patients with severe G6PD deficiency (see Contraindications). In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. Discontinue the use of primaquine phosphate promptly if signs suggestive of hemolytic anemia occur (darkening of the urine, marked fall of hemoglobin or erythrocytic count). Hemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia, and Oceania. People from these regions have a greater tendency to develop hemolytic anemia (due to a congenital deficiency of erythrocytic G6PD) while receiving primaquine and related drugs. *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). **PRECAUTIONS** *Blood Monitoring* Since anemia, methemoglobinemia, and leukopenia have been observed following administration of large doses of primaquine, the adult dosage of 1 tablet (= 15 mg base) daily for fourteen days should not be exceeded. In G6PD normal patients it is also advisable to perform routine blood examinations (particularly blood cell counts and hemoglobin determinations) during therapy.

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Blue text represents the most recent addtions and/or changes since last posted version.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					ADVERSE REACTIONS *Hematologic* Leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals. **OVERDOSAGE** Symptoms of overdosage of primaquine phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia, and anemia. The most striking symptoms are granulocytopenia and acute hemolytic anemia in G6PD deficient patients. Acute hemolysis occurs, but patients recover completely if the dosage is discontinued.
008316, 06/22/2017	Primaquine (2)	Infectious Diseases	CYB5R	Precautions, Adverse Reactions	**PRECAUTIONS** *Blood Monitoring* (…) If primaquine phosphate is prescribed for an individual who has shown a previous idiosyncratic reaction to primaquine phosphate as manifested by hemolytic anemia, methemoglobinemia, or leukopenia; an individual with a family or personal history of hemolytic anemia or nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency, the person should be observed closely. In all patients, the drug should be discontinued immediately if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs. **ADVERSE REACTIONS** *Hematologic* Leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.
007898	Probenecid	Rheumatology	G6PD	Adverse Reactions	Labeling not electronically available on Drugs@FDA
020545	Procainamide	Cardiology	Nonspecific (NAT)	Adverse Reactions, Clinical Pharmacology	Labeling not electronically available on Drugs@FDA
021416, 11/02/2018	Propafenone	Cardiology	CYP2D6	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** (…) The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor [see Warnings and Precautions (5.4) and Drug Interactions (7.1)]. **5 WARNINGS AND PRECAUTIONS** **5.4 Drug Interactions: Simultaneous Use with Inhibitors of Cytochrome P450 Isoenzymes 2D6 and 3A4** Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6 activity and to a somewhat lesser extent in other demographic groups. Drugs that inhibit these CYP pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP2D6; ketoconazole, erythromycin, saquinavir, and grapefruit juice for CYP3A4; and amiodarone and tobacco smoke for CYP1A2) can be expected to cause increased plasma levels of propafenone. Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor. **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 Pharmacokinetic** *Metabolism* There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5- hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers. As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers 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-hydroxymetabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The larger inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity [see Dosage and Administration (2)]. *Inter-Subject Variability* With propafenone, there is a considerable degree of inter- subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear 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.
021438, 11/19/2013	**Propranolol**	Cardiology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism and Elimination* In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance to 4-hydroxy propranolol was significantly higher and to naphthyloxylactic acid was significantly lower in EMs than PMs.
073644, 07/17/2014	**Protriptyline**	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Drugs Metabolized by Cytochrome P450 2D6* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced 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). (…)
089338, 02/02/2010	**Quinidine**	Cardiology	CYP2D6	Precautions	**PRECAUTIONS** (…) Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers". When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the case of prodrugs whose actions are actually mediated by P450IID6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers. Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6. (…)
021799, 06/19/2019	**Quinine Sulfate (1)**	Infectious Diseases	G6PD	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.3 Hemolytic Anemia** Acute hemolytic anemia has been reported in patients receiving quinine for treatment of malaria, including patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The cause for the acute hemolytic anemia in quinine-treated patients with malaria and its potential relationship with G6PD deficiency has not been determined. Closely monitor hemoglobin and hematocrit during quinine treatment. Quinine should be discontinued if patients develop acute hemolytic anemia.
021799, 06/19/2019	**Quinine Sulfate (2)**	Infectious Diseases	CYP2D6	Drug Interactions	**7 DRUG INTERACTIONS** **7.2 Effects of Quinine on the Pharmacokinetics of Other Drugs** *Desipramine (CYP2D6 substrate)* Quinine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. (…)
020973, 06/07/2018	**Rabeprazole**	Gastroenterology	CYP2C19	Drug Interactions, Clinical Pharmacology	**7 DRUG INTERACTIONS** *Tacrolimus* Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. (See Table 3) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism*

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Blue text represents the most recent addtions and/or changes since last posted version.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					(…) 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 delayedrelease 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.
020815, 06/27/2018	**Raloxifene**	Oncology	ESR (Hormone Receptor)	Clinical Studies	**14 CLINICAL STUDIES** **14.3 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis** MORE Trial The effect of EVISTA on the incidence of breast cancer was assessed as a secondary safety endpoint in a randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women [see Clinical Studies (14.1)]. After 4 years, EVISTA, 60 mg administered once daily, reduced the incidence of all breast cancers by 62%, compared with placebo (HR 0.38, 95% CI 0.22-0.67). EVISTA reduced the incidence of invasive breast cancer by 71%, compared with placebo (ARR 3.1 per 1000 women-years); this was primarily due to an 80% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. (See Table 7) CORE Trial The effect of EVISTA on the incidence of invasive breast cancer was evaluated for 4 additional years in a follow-up study conducted in a subset of postmenopausal women originally enrolled in the MORE osteoporosis treatment trial. Women were not re-randomized; the treatment assignment from the osteoporosis treatment trial was carried forward to this study. EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 56%, compared with placebo (ARR 3.0 per 1000 women-years); this was primarily due to a 63% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. There was no reduction in the incidence of ERnegative breast cancer. In the osteoporosis treatment trial and the follow-up study, there was no difference in incidence of noninvasive breast cancer between the EVISTA and placebo groups. In a subset of postmenopausal women followed for up to 8 years from randomization in MORE to the end of CORE, EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 60% in women assigned EVISTA (N=1355) compared with placebo (N=1286) (HR 0.40, 95% CI 0.21, 0.77; ARR 1.95 per 1000 womenyears); this was primarily due to a 65% reduction in the incidence of ER-positive invasive breast cancer in the EVISTA group compared with placebo. (See Table 7) RUTH Trial EVISTA, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 44% compared with placebo [absolute risk reduction (ARR) 1.2 per 1000 women-years]; this was primarily due to a 55% reduction in estrogen receptor (ER)-positive invasive breast cancer in the EVISTA group compared with placebo (ARR 1.2 per 1000 womenyears). There was no reduction in ER-negative invasive breast cancer. Table 8 presents efficacy and selected safety outcomes. (See Table 8) (…)
022145, 03/05/2018	**Raltegravir**	Infectious Diseases	UGT1A1	Clinical Pharmacology	**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 UGT 1A1 genotype polymorphisms.
125477, 08/14/2018	**Ramucirumab (1)**	Oncology	EGFR	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Non-Small Cell Lung Cancer** **(…)** Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 82% were White and 13% were Asian; 32% had ECOG PS 0; 73% had nonsquamous histology and 26% had squamous histology. In addition to platinum chemotherapy (99%), the most common prior therapies were pemetrexed (38%), gemcitabine (25%), taxane (24%), and bevacizumab (14%). Twenty-two percent of patients received prior maintenance therapy. Tumor EGFR status was unknown for the majority of patients (65%). Where tumor EGFR status was known (n=445), 7.4% were positive for EGFR mutation (n=33). No data were collected regarding tumor ALK rearrangement status. (…)
125477, 08/14/2018	**Ramucirumab (2)**	Oncology	RAS	Clinical Studies	**14 CLINICAL STUDIES** **14.3 Colorectal Cancer** (…) Randomization was stratified by geographic region, tumor KRAS status, and time to disease progression after beginning first-line treatment (<6 months versus ≥6 months).

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

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					Demographic and baseline characteristics were similar between treatment arms. Median age was 62 years; 57% of patients were men; 76% were White and 20% Asian; 49% had ECOG PS 0; 49% of patients had KRAS mutant tumors; and 24% of patients had <6 months from time to disease progression after beginning first-line treatment. (…)
103946, 09/14/2017	**Rasburicase (1)**	Oncology	G6PD	Boxed Warning, Contraindications, Warnings and Precautions	**BOXED WARNING** WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS *Hemolysis* Do not administer Elitek to patients with glucose-6- phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Elitek if hemolysis occurs. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek therapy (4, 5.2). **4 CONTRAINDICATIONS** Elitek is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) [see Boxed Warning, Warnings and Precautions (5.2)]. **5 WARNINGS AND PRECAUTIONS** **5.2 Hemolysis** Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in <1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Boxed Warning, Contraindications (4)].
103946, 09/14/2017	**Rasburicase (2)**	Oncology	CYB5R	Boxed Warning, Contraindications, Warnings and Precautions	**BOXED WARNING** WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS *Methemoglobinemia* Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek if methemoglobinemia occurs (4, 5.3). **4 CONTRAINDICATIONS** Elitek is contraindicated in patients with a history of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase [see Boxed Warning, Warnings and Precautions (5)]. **5 WARNINGS AND PRECAUTIONS** **5.3 Methemoglobinemia** In clinical studies, methemoglobinemia occurred in <1% patients receiving Elitek. These included cases of serious hypoxemia requiring intervention with medical support measures. It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia. Immediately and permanently discontinue Elitek administration in any patient identified as having developed methemoglobinemia. Institute appropriate monitoring and support measures (e.g., transfusion support, methylene-blue administration) [see Boxed Warning, Contraindications (4)].
203085, 06/14/2018	**Regorafenib**	Oncology	RAS	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Colorectal Cancer** STIVARGA is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wildtype, an anti-EGFR therapy. **14 CLINICAL STUDIES** **14.1 Colorectal Cancer** **(…)** Baseline demographics were: median age 61 years, 61% men, 78% White, and all patients had an ECOG performance status of 0 or 1. The primary sites of disease were colon (65%), rectum (29%), or both (6%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutationnegative tumors received panitumumab or cetuximab. (…)
209092, 07/18/2018	**Ribociclib (1)**	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** KISQALI is indicated in combination with: • an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or • fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy. **6 ADVERSE REACTIONS** **MONALEESA-2: KISQALI in combination with Letrozole** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* The safety data reported below are based on MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥12 months. (…)

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Last Updated: 06/2019

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					MONALEESA-7: KISQALI in combination with an Aromatase Inhibitor *Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a non-steroidal aromatase inhibitors (NSAI) or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. (…) **MONALEESA-3: KISQALI in combination with Fulvestrant** *Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy* The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. (…) **14 CLINICAL STUDIES** **MONALEESA-2: KISQALI in Combination with Letrozole** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* MONALEESA-2 was a randomized, double-blind, placebo-controlled, multicenter clinical study of KISQALI plus letrozole versus placebo plus letrozole conducted in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. (…) **MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor** *Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* MONALEESA-7 was a randomized, double-blind, placebo-controlled study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.(…) **MONALEESA-3: KISQALI in Combination with Fulvestrant** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy* MONALEESA-3 was a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)
209092, 07/18/2018	**Ribociclib (2)**	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clincal Studies	**1 INDICATIONS AND USAGE** KISQALI is indicated in combination with: • an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or • fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy. **6 ADVERSE REACTIONS** **MONALEESA-2: KISQALI in combination with Letrozole** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* The safety data reported below are based on MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥12 months. (…) **MONALEESA-7: KISQALI in combination with an Aromatase Inhibitor** *Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a non-steroidal aromatase inhibitors (NSAI) or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. (…) **MONALEESA-3: KISQALI in combination with Fulvestrant** *Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy* The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. (…) **14 CLINICAL STUDIES** **MONALEESA-2: KISQALI in Combination with Letrozole** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* MONALEESA-2 was a randomized, double-blind, placebo-controlled, multicenter clinical study of KISQALI plus letrozole versus placebo plus letrozole conducted in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. (…) **MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor** *Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy* MONALEESA-7 was a randomized, double-blind, placebo-controlled study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.(…) **MONALEESA-3: KISQALI in Combination with Fulvestrant** *Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy*

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Last Updated: 06/2019

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					MONALEESA-3 was a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. (…)
020272, 01/25/2019	**Risperidone**	Psychiatry	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Absorption* Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution. Pharmacokinetic studies showed that RISPERDAL M-TAB Orally Disintegrating Tablets and RISPERDAL Oral Solution are bioequivalent to RISPERDAL Tablets. Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers). *Metabolism* (…) CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers. Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone [see Drug Interactions (7)]. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given RISPERDAL do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone [see Drug Interactions (7)]. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely [see Drug Interactions (7)]. (…) *Excretion* Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.
103705, 01/25/2019	**Rituximab**	Oncology	MS4A1 (CD20 antigen)	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Non–Hodgkin's Lymphoma (NHL)** Rituxan (rituximab) is indicated for the treatment of patients with: • Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. • Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy. • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy. • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. **1.2 Chronic Lymphocytic Leukemia (CLL)** Rituxan (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL. **2 DOSAGE AND ADMINISTRATION** **2.2 Recommended Dos e for Non-Hodgkin's Lymphoma (NHL)** The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules: • *Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL* Administer once weekly for 4 or 8 doses. • *Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL* Administer once weekly for 4 doses. • *Previously Untreated, Follicular, CD20-Positive, B-Cell NHL* Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses. • *Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy* Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

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Last Updated: 06/2019

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					• *Diffuse Large B-Cell NHL* Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience in Lymphoid Malignancies** *Cytopenias and hypogammaglobulinemia* (…) Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [See Clinical Studies (14.1)]. Most patients received Rituxan 375 mg/m^2 weekly for 4 doses. (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** *Low-Grade or Follicular Non-Hodgkin's Lymphoma* Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. **14 CLINICAL STUDIES** **14.1 Relaps ed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL** The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients. (…) **14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL** The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients. (…)
022406, 01/15/2019	**Rivaroxaban**	Cardiology	F5 (Factor V Leiden)	Clinical Studies	**14 CLINICAL STUDIES** **14.3 Reduction in the Risk of Recurrence of DVT and/or PE** EINSTEIN CHOICE Study (…) A total of 2275 patients were randomized and followed on study treatment for a mean of 290 days for the XARELTO and aspirin treatment groups. The mean age was approximately 59 years. The population was 56% male, 70% Caucasian, 14% Asian and 3% Black. In the EINSTEIN CHOICE study, 51% of patients had DVT only, 33% had PE only, and 16% had PE and DVT combined. Other risk factors included idiopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophilic conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%). (…)
020533, 11/02/2018	**Ropivacaine (1)**	Anesthesiology	G6PD	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6- phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
020533, 11/02/2018	**Ropivacaine (2)**	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings	**WARNINGS** **Methemoglobinemia** Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6- phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. (…)
021366, 11/09/2018	**Rosuvastatin**	Endocrinology	SLCO1B1	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T > C). The frequency of this genotype (i.e., SLCO1B1 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established.
209115, 04/06/2018	**Rucaparib (1)**	Oncology	BRCA	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies	**1 INDICATIONS AND USAGE** **1.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies** Rubraca is indicated for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)- associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.3 Patient Selection for Treatment of BRCA-mutated Ovarian Cancer**

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Last Updated: 06/2019

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					Select patients for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer with Rubraca based on the presence of a deleterious BRCA mutation (germline and/or somatic) [see Indications and Usage (1.2) and Clinical Studies (14.2)]. Information on the FDA-approved test for the detection of a tumor BRCA mutation in patients with ovarian cancer is available at: http://www.fda.gov/CompanionDiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** (…) Rubraca 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two openlabel, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had BRCA-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197). (…) **8 USE IN SPECIFIC POPULATIONS** **8.5 Geriatric Use** In clinical studies 40% (297/749) of patients with ovarian cancer treated with Rubraca were 65 years of age or older and 9% (65/749) were 75 years or older. Grade 3-4 adverse reactions occurred in 65% of patients 65 years or older and in 63% of patients 75 years or older. For patients 65 years or older, the most common Grade 3-4 adverse reactions were anemia, fatigue/asthenia, and ALT/AST increase. No major differences in safety were observed between these patients and younger patients for the maintenance treatment of recurrent ovarian cancer or for the treatment of BRCA-mutated ovarian cancer after two or more chemotherapies. **14 CLINICAL STUDIES** (…) Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564), and the FoundationFocus™ CDx BRCA LOH test (n=518). Of the samples evaluated with both tests, homologous recombination deficiency (HRD) positive status (as defined by the presence of a deleterious BRCA mutation or high genomic loss of heterozygosity) was confirmed 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 tBRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the tBRCA patients had a germline BRCA mutation and 30% (56/186) had a somatic BRCA mutation. ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rubraca as compared with placebo in all patients, and in the HRD and tBRCA subgroups. Results from a blinded independent radiology review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (with 22% of events). (see Table 6, Figures 1, 2, and 3) **14.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies** The efficacy of Rubraca was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 10 (NCT01482715) and ARIEL2 (NCT01891344), in patients with advanced BRCA-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rubraca 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and IRR according to RECIST v1.1. The median age of the patients was 59 years (range: 33 to 84), the majority were White (78%), and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had received 3 or more prior lines of platinum-based chemotherapy. There were 18/106 patients (17%) who had deleterious BRCA mutations detected in tumor tissue and not in whole blood 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, 41]) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation.
209115, 04/06/2018	**Rucaparib (2)**	Oncology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Specific Populations* *CYP Enzyme Polymorphism* Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.
209115, 04/06/2018	**Rucaparib (3)**	Oncology	CYP1A2	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Specific Populations* *CYP Enzyme Polymorphism* Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.
209115, 04/06/2018	**Rucaparib (4)**	Oncology	Homologous Recombination Deficiency	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Maintenance Treatment of Recurrent Ovarian Cancer** (…) Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564), and the FoundationFocus™ CDx BRCA LOH test (n=518). Of the samples evaluated with both tests, homologous recombination deficiency (HRD) positive status (as defined by the presence of a deleterious BRCA mutation or high genomic loss of heterozygosity) was confirmed by the FoundationFocus™ CDx BRCA LOH test for 94% (313/332) of HRD-positive patients determined by the

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					CTA; and of these, tumor BRCA (tBRCA) mutant status was confirmed by the FoundationFocus™ CDx BRCA LOH test for 99% (177/178) of tBRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the tBRCA patients had a germline BRCA mutation and 30% (56/186) had a somatic BRCA mutation. ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rubraca as compared with placebo in all patients, and in the HRD and tBRCA subgroups. Results from a blinded independent radiology review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (with 22% of events). (See Table 6 and Figure 2).
020478, 04/27/2017	Sevoflurane	Anesthesiology	RYR1	Warnings	**WARNINGS** Malignant Hyperthermia In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Sevoflurane can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia, and hypovolemia. In clinical trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these cases have been fatal. Treatment of malignant hyperthermia includes discontinuation of triggering agents (e.g., sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), and application of supportive therapy. Supportive therapy may include efforts to restore body temperature, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.
205123, 11/09/2017	Simeprevir	Infectious Diseases	IFNL3 (IL28B)	Clinical Pharmacology, Clinical Studies	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C [cytosine] to T [thymine] substitution) is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor. Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with OLYSIO-containing regimens. (See Table 12 and 13) **14 CLINICAL STUDIES** **14.2 OLYSIO in Combination with Sofosbuvir** *Adult Subjects with HCV Genotype 1 Infection* (…) These 59 subjects had a median age of 57 years (range 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, and 24% Black or African American; 46% had a BMI greater than or equal to 30 kg/m2 ; the median baseline HCV RNA level was 6.75 log10 IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0-F1, F2 and F3, respectively, and 29% had METAVIR fibrosis score F4 (cirrhosis); 75% 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 genotype 1-infected subjects without cirrhosis who were treatment-naïve or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred fifty-five subjects received 12 weeks of OLYSIO with sofosbuvir. The 155 subjects without cirrhosis receiving 12 weeks of OLYSIO with sofosbuvir had a median age of 56 years (range 19 to 70 years; with 7% above 65 years); 53% 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; 74% were treatment-naïve and 26% were treatment-experienced. (…) (…) Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%] respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]), and subjects with IL28B CC and non-CC genotypes (43/43 [100%] and 107/112 [96%], respectively). **14.3 OLYSIO in Combination with Peg-IFN-alfa and RBV** *Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection* (…) In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the OLYSIO and placebo treatment groups. In the pooled analysis of trials (QUEST 1 and QUEST 2), the 785 enrolled subjects had a median age of 47 years (range: 18 to 73 years; with 2% above 65 years); 56% were male; 91% were White, 7% Black or African American, 1% Asian, and 17% Hispanic; 23% had a body mass index (BMI) greater than or equal to 30 kg/m2 ; 78% had baseline HCV RNA levels greater than 800000 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, 56% IL28B CT genotype, and 15% IL28B TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a; in QUEST 2, 69% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b. Table 17 shows the response rates in treatment-naïve adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR12 rates were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. (See Table 17) (…) *Treatment-Naïve East Asian Subjects with HCV Genotype 1 Infection* (…) These 304 subjects had a median age of 45 years (range: 18 to 68 years; with 2% above 65 years); 49% were male; all were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater or equal to 30 kg/m2 ; 84% had baseline HCV RNA levels greater than

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

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					800000 IU/mL; 82% had METAVIR fibrosis score F0, F1 or F2, 12% METAVIR fibrosis score F3, and 6% METAVIR fibrosis score F4 (cirrhosis); 1% had HCV genotype 1a, and 99% HCV genotype 1b; less than 1% of the overall population had Q80K polymorphism at baseline; 79% had IL28B CC genotype, 20% IL28B CT genotype, and 1% IL28B TT genotype. Demographics and baseline characteristics were balanced across the OLYSIO 150 mg and placebo treatment groups. (…) *Adult Subjects with HCV Genotype 1 Infection who Failed Prior Peg-IFN-alfa and RBV Therapy* (…) Demographics and baseline characteristics were balanced between the OLYSIO and placebo treatment groups. The 393 subjects enrolled in the PROMISE trial had a median age of 52 years (range: 20 to 71 years; with 3% above 65 years); 66% were male; 94% were White, 3% Black or African American, 2% Asian, and 7% Hispanic; 26% had a BMI greater than or equal to 30 kg/m2 ; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 69% had METAVIR fibrosis score F0, F1 or F2, 15% METAVIR fibrosis score F3, and 15% METAVIR fibrosis score F4 (cirrhosis); 42% had HCV genotype 1a, and 58% HCV genotype 1b; 24% had IL28B CC genotype, 64% IL28B CT genotype, and 12% IL28B TT genotype; 13% of the overall population and 31% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. The prior IFN-based HCV therapy was Peg-IFN-alfa-2a/RBV (68%) or Peg-IFN-alfa-2b/RBV (27%). (…) (…) SVR12 rates were higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype/subtype, baseline HCV RNA load (less than or equal to 800000 IU/mL, greater than 800000 IU/mL), prior HCV therapy, METAVIR fibrosis score, and IL28B genotype. Table 20 shows the SVR rates by METAVIR fibrosis score. (…) (…) In this trial, 66 subjects received 12 weeks of 150 mg OLYSIO in combination with Peg-IFN-alfa-2a and RBV for 48 weeks, and 66 subjects received placebo in combination with Peg-IFN-alfa-2a and RBV for 48 weeks. These 132 subjects had a median age of 49 years (range: 20 to 66 years; with 1% 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 800000 IU/mL; 64% had METAVIR fibrosis score F0, F1, or F2, 18% 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 6% 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, 19% 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); 79% were male; 72% were White, 28% Black or African American, and 7% Hispanic; 14% had a BMI greater than or equal to 30 kg/m2 ; 60% had baseline 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 4d; 8% had IL28B CC genotype, 58% IL28B CT genotype, and 35% IL28B TT genotype; 33% (n=35) were treatment-naïve HCV subjects, 21% (n=22) prior relapsers, 9% (n=10) prior partial responders, and 37% (n=40) prior null responders. (…)
209884, 03/26/2019	**Siponimod**	Neurology	CYP2C9	Dosage and Administration, Contraindications, Drug Interactions, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.1 Assessments Prior to First Dose of MAYZENT** Before initiation of treatment with MAYZENT, assess the following: CYP2C9 Genotype Determination Test patients for CYP2C9 variants to determine CYP2C9 genotype [see Dosage and Administration (2.2, 2.3), Contraindications (4), and Use in Specific Populations (8.6)]. An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available. **2.2 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2** Maintenance Dosage After treatment titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 2 mg taken orally once daily starting on Day 6. Dosage adjustment is required in patients with a CYP2C9 *1/*3 or *2/*3 genotype [see Dosage and Administration (2.3)]. Treatment Initiation Initiate MAYZENT with a 5-day titration, as shown in Table 1 [see Warnings and Precautions (5.3)]. A starter pack should be used for patients who will be titrated to the 2-mg maintenance dosage [see How Supplied/Storage and Handling (16.1, 16.2)]. (See Table 1) If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen. **2.3 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3** Maintenance Dosage In patients with a CYP2C9 *1/*3 or *2/*3 genotype, after treatment titration (see Treatment Initiation), the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 5. Treatment Initiation Initiate MAYZENT with a 4-day titration, as shown in Table 2 [see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]. Do not use the starter pack for patients who will be titrated to the 1-mg maintenance dosage. (See Table 2)

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

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					If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen. **4 CONTRAINDICATIONS** MAYZENT is contraindicated in patients who have: • A CYP2C9*3/*3 genotype [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)] (…) **7 DRUG INTERACTIONS** **7.6 CYP2C9 and CYP3A4 Inducers** Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer. Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers. Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and*2/*3 genotype [see Clinical Pharmacology (12.3)]. **8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2C9 Genotype** Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4% 0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9 *1/*3 or *2/*3 genotype because of an increase in exposure to siponimod [see Dosage and Administration (2.3) and Clinical Pharmacology (12.5)]. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Immune System MAYZENT induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, caused by the reversible sequestration of lymphocytes in lymphoid tissues. With continued daily dosing, the lymphocyte count continues to decrease, reaching a nadir median (90% CI) lymphocyte count of approximately 0.560 (0.271-1.08) cells/nL in a typical CYP2C9*1/*1 or *1/*2, non-Japanese patient, corresponding to 20% to 30% of baseline. Low lymphocyte counts are maintained with chronic daily dosing [see Warnings and Precautions (5.1)]. Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. After stopping MAYZENT treatment, residual lowering effects on peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose [see Warnings and Precautions (5.1)]. **12.3 Pharmacokinetics** Drug Interaction Studies *Siponimod as an Object of Interaction* CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. Physiologically based PK modeling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated. *Coadministration of Siponimod with CYP2C9 and CYP3A4 Inhibitors* The coadministration of fluconazole (moderate CYP2C9 and CYP3A4 dual inhibitor) 200 mg daily at steady-state and a single dose of siponimod 4 mg in CYP2C9*1/*1 healthy volunteers led to a 2-fold increase in the AUC of siponimod. Mean siponimod terminal half-life was increased by 50%. Fluconazole led to a 2-to 4-fold increase in the AUCtau,ss of siponimod across different CYP2C9 genotypes, according to in silico evaluation [see Drug Interactions (7.5)]. *Coadministration of Siponimod with CYP2C9 and CYP3A4 Inducers* The coadministration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampin (strong CYP3A4 and moderate CYP2C9 dual inducer) decreased siponimod AUCtau,ss and Cmax,ss by 57% and 45%, respectively in CY2C9*1/*1 subjects. Rifampin and efavirenz (moderate CYP3A4 inducer) reduced the AUCtau,ss of siponimod by up to 78% and up to 52%, respectively, across CYP2C9 genotypes, according to in silico evaluation [see Drug Interactions (7.6)]. *Oral Contraceptives* The effects of coadministration of siponimod 2 mg and 4 mg (twice the recommended dosage) once daily with a monophasic oral contraceptive (OC) containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were assessed in 24 healthy female subjects (18 to 40 years of age; CYP2C9*1/*1 genotype). There were no clinically relevant effects on the PK or PD of the OC. No interaction studies have been performed with OCs containing other progestagens; however, an effect of siponimod on their exposure is not expected. **12.5 Pharmacogenomics** The CYP2C9 genotype has a significant impact on siponimod metabolism. After a single dose of 0.25 mg siponimod, AUCinf and AUClast was approximately 2- and 4-fold higher in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes, respectively, while there was only a minor increase of Cmax by 21% and 16%, respectively, compared to extensive metabolizers (CYP2C9*1/*1). Mean half-life is prolonged in CYP2C9*2/*3 and CYP2C9*3/*3 carriers (51 hours and 126 hours, respectively). An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9*1/*1 and CYP2C9*1/*2) MS patients after multiple oral administrations of siponimod. Cl/F is 2.5, 1.9, 1.6, and 0.9 L/h in subjects with the CYP2C9*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 genotypes respectively. The resultant increase in siponimod AUC was approximatively 25, 61, 91, and 285% higher in CYP2C9*2/*2, CYP2C9*1/*3,

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Last Updated: 06/2019

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					CYP2C9*2/*3, and CYP2C9*3/*3 subjects, respectively, as compared to CYP2C9*1/*1 subjects [see Dosage and Administration (2.1, 2.3) and Contraindications (4)]. As the apparent clearance estimated for CYP2C9*1*2 subjects is comparable to that of CYP2C9*1/*1 subjects, similar siponimod exposure is expected for both genotypes.
203922, 10/19/2017	Sodium Nitrite (1)	Toxicology	G6PD	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.6 G6PD Deficiency** Because patients with G6PD deficiency are at increased risk of a hemolytic crisis with sodium nitrite administration, alternative therapeutic approaches should be considered in these patients. Patients with known or suspected G6PD deficiency should be monitored for an acute drop in hematocrit. Exchange transfusion may be needed for patients with G6PD deficiency who receive sodium nitrite.
203922, 10/19/2017	Sodium Nitrite (2)	Toxicology	Nonspecific (Congenital Methemoglobinemia)	Boxed Warning, Warnings and Precautions	**BOXED WARNING** **WARNING: LIFE THREATENING HYPOTENSION AND METHEMOGLOBIN FORMATION** Sodium nitrite can cause serious adverse reactions and death in humans, even at doses less than twice the recommended therapeutic dose. Sodium nitrite causes hypotension and methemoglobin formation, which diminishes oxygen carrying capacity. Hypotension and methemoglobin formation can occur concurrently or separately. Because of these risks, sodium nitrite should be used to treat acute life-threatening cyanide poisoning and be used with caution in patients where the diagnosis of cyanide poisoning is uncertain. Patients should be closely monitored to ensure adequate perfusion and oxygenation during treatment with sodium nitrite. Alternative therapeutic approaches should be considered in patients known to have diminished oxygen or cardiovascular reserve (e.g., smoke inhalation victims, pre-existing anemia, cardiac or respiratory compromise), and those at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency) as they are at greater risk for potentially life-threatening adverse events related to the use of sodium nitrite. [see Warnings and Precautions (5.1 and 5.2)] **5 WARNINGS AND PRECAUTIONS** **5.1 Hypotension** Sodium nitrite has been associated with severe hypotension, methemoglobinemia, and death at doses less than twice recommended therapeutic doses. Hypotension may occur concurrently or separately. Sodium nitrite should be used to treat life-threatening cyanide poisoning. When the diagnosis of cyanide poisoning is uncertain and/or the patient is not in extremis, special consideration should be given to administration of sodium nitrite if the patient is known or suspected to have diminished oxygen or cardiovascular reserve (e.g., smoke inhalation victims, pre-existing anemia, substantial blood loss, cardiac or respiratory compromise) or to be at higher risk of developing methemoglobinemia (e.g., congenital methemoglobin reductase deficiency). **5.2 Methemoglobinemia** Supportive care alone may be sufficient treatment without administration of antidotes for many cases of cyanide intoxication, particularly in conscious patients without signs of severe toxicity. Monitor patients closely to ensure adequate perfusion and oxygenation during treatment with sodium nitrite. Monitor methemoglobin levels and administer oxygen during treatment with sodium nitrite whenever possible. When sodium nitrite is administered to humans a wide range of methemoglobin concentrations occur. (…)
020572, 03/31/2009	Sodium Phenylbutyrate	Inborn Errors of Metabolism	ASS1, CPS1, OTC (Urea Cycle Disorders)	Indications and Usage, Dosage and Administration	**INDICATIONS AND USAGE** BUPHENYL® is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a lifethreatening emergency. (…) (…) Those who had IQ tests administered had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100% (14/14 patients tested); argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested); and carbamylphosphate synthetase deficiency, 57% (4/7 patients tested). (…) (…) In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98%. (…) **DOSAGE AND ADMINISTRATION** For oral use only. The use of BUPHENYL® Tablets is indicated for children weighing more than 20 kg and for adults. The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450– 600 mg/kg/day in patients weighing less than 20 kg, or 9.9–13.0 g/m2 /day in larger patients. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day). (…) **NUTRITIONAL MANAGEMENT** (…) At the recommended dose of sodium phenylbutyrate, it is suggested that infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period. Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake. From 4 months to 1 year of age, it is recommended that the infant receive at least 1.4 g/kg/day, but 1.7 g/kg/day is advisable. From 1 to 3 years of age, the protein intake should not be less than 1.2 g/kg/day; 1.4 g/kg/day is advisable during this period. For neonatal-onset patients with carbamylphosphate synthetase deficiency or ornithine transcarbamylase deficiency who are at least 6 months of age, it is recommended that the daily protein intake be equally divided between natural protein and supplemental essential amino acids.

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Last Updated: 06/2019

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					Patients with argininosuccinic acid synthetase deficiency and those with late-onset disease (partial deficiencies, including females heterozygous for ornithine transcarbamylase), initially may receive a diet containing the age-determined minimal daily natural protein allowance. The protein intake may be increased as tolerated and determined by plasma glutamine and other amino acid levels. However, many patients with partial deficiencies avoid dietary protein. Citrulline supplementation is required and recommended for patients diagnosed with neonatal-onset deficiency of carbamylphosphate synthetase or ornithine transcarbamylase; citrulline daily intake is recommended at 0.17 g/kg/day or 3.8 g/m2 /day. The free-base form of arginine may be used instead of citrulline in patients with milder forms of carbamylphosphate synthetase and ornithine transcarbamylase deficiency (daily intake is recommended at 0.17 g/kg/day or 3.8 g/m2 /day). Arginine supplementation is needed for patients diagnosed with deficiency of argininosuccinic acid synthetase; arginine (free base) daily intake is recommended at 0.4–0.7 g/kg/day or 8.8–15.4 g/m2 /day.
204671, 10/23/2018	**Sofosbuvir**	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Clinical Trials in Subjects with Genotype 1 or 4 HCV** *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 interferonbased treatment (Table 9). The SVR12 rate in the NEUTRINO trial in genotype 1 subjects with IL28B non-C/C alleles, HCV RNA greater than 800,000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52). (See Table 9) **14.4 Clinical Trials in Subjects Coinfected with HCV and HIV-1** (…) In subjects with HCV genotype 1 infection, the SVR12 rate was 82% (74/90) in subjects with genotype 1a infection and 54% (13/24) in subjects with genotype 1b infection, with relapse accounting for the majority of treatment failures. SVR12 rates in subjects with HCV genotype 1 infection were 80% (24/30) in subjects with baseline IL28B C/C allele and 75% (62/83) in subjects with baseline IL28B non-C/C alleles. (…) **14.5 Clinical Trial in Pediatrics** The efficacy of SOVALDI in HCV-infected pediatric subjects 12 years of age and older was evaluated in 50 subjects with HCV genotype 2 (N = 13) or genotype 3 (N = 37) in a Phase 2, open label clinical trial. Subjects with HCV genotype 2 or 3 infection in the trial were treated with SOVALDI and weight-based ribavirin for 12 or 24 weeks, respectively [see Dosage and Administration (2.3)]. Of the 50 treated subjects, the median age was 15 years (range: 12 to 17); 42% of the subjects were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 61 kg (range: 30 to 101 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 74% of subjects had non-CC IL28B alleles (CT or TT); and no subjects had known cirrhosis. The majority of subjects (69%) had been infected through vertical transmission. The SVR12 rate was 100% (13/13) in genotype 2 subjects and 97% (36/37) in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse.
208341, 11/09/2017	**Sofosbuvir and Velpatasvir**	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Clinical Trials in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis** *Genotype 1, 2, 4, 5, and 6 HCV Infected Adults (ASTRAL-1)* (…) Demographics and baseline characteristics were balanced between the EPCLUSA and placebo group. Of the 740 treated subjects, the median age was 56 years (range: 18 to 82); 60% of the subjects were male; 79% were White, 9% were Black; 21% had a baseline body mass index at least 30 kg/m2 ; the proportions of subjects with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5%, and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced. (…) *Genotype 2 HCV Infected Adults (ASTRAL-2)* (…) Demographics and baseline characteristics were balanced across the two treatment groups. Of the 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); 80% had baseline HCV RNA levels at least 800,000 IU/mL; 14% had compensated cirrhosis; and 15% were treatment-experienced. (…) *Genotype 3 HCV Infected Adults (ASTRAL-3)* (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 552 treated subjects, the median age was 52 years (range: 19 to 76); 62% of the subjects were male; 89% were White; 9% were Asian; 20% had a baseline body mass index at least 30 kg/m2 ; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels at least 800,000 IU/mL; 30% had compensated cirrhosis; and 26% were treatment-experienced. (…) **14.3 Clinical Trial in Subjects Coinfected with HCV and HIV-1** (…)Of the 106 treated subjects, the median age was 57 years (range: 25 to 72); 86% of the subjects were male; 51% were White; 45% were Black; 22% had a baseline body mass index at least 30 kg/m2 ; the proportions of patients with genotype 1, 2, 3, or 4 HCV infection were 74%; 10%; 11%, and 5% respectively; no subjects with genotype 5 or 6 HCV were treated with EPCLUSA; 77% had non- CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels of at least 800,000 IU/mL; 18% had compensated cirrhosis; and 29% were treatment experienced. The overall mean CD4+ count was 598 cells/µL (range: 183−1513 cells/µL) and 57% of subjects had CD4+ counts > 500 cells/µL. (…) **14.4 Clinical Trials in Subjects with Decompensated Cirrhosis** (…) Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White, 6% were Black; 42% had a baseline body mass index at least 30 kg/m2 . The proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 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 treatmentexperienced; 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. (…)

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

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209195, 11/09/2017	Sofosbuvir, Velpatasvir, and Voxilaprevir	Infectious Diseases	IFNL3 (IL28B)	Clinical Studies	**CLINICAL STUDIES** **14.2 Clinical Trials in HCV DAA-Experienced Subjects** *NS5A Inhibitor-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis (POLARIS-1)* (…) Demographics and baseline characteristics were generally balanced across treatment groups. Of the 415 treated subjects, the median age was 59 years (range: 27 to 84); 77% of the subjects were male; 81% were White; 14% were Black; 6% were Hispanic or Latino; 33% had a baseline body mass index at least 30 kg/m^2; the majority of subjects had genotype 1 (72%) or genotype 3 (19%) HCV infection; 82% had a non-CC IL28B genotype (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; and 41% had compensated cirrhosis. (…) *DAA-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis Who Had Not Received An NS5A Inhibitor (POLARIS-4)* (…) Demographics and baseline characteristics were generally balanced across treatment groups. Of the 333 treated subjects, the median age was 58 years (range: 24 to 85); 77% of the subjects were male; 87% were White, 9% were Black; 8% were Hispanic or Latino; 35% had a baseline body mass index at least 30 kg/m^2; 81% had non-CC IL28B genotypes (CT or TT); 75% had baseline HCV RNA levels at least 800,000 IU/mL; and 46% had compensated cirrhosis. (…)
019998, 10/02/2018	Succimer	Hematology	G6PD	Clinical Pharmacology	**CLINICAL PHARMACOLOGY** (…) In addition to the controlled studies, approximately 250 patients with lead poisoning have been treated with succimer either orally or parenterally in open U.S. and foreign studies with similar results reported. Succimer has been used for the treatment of lead poisoning in one patient with sickle cell anemia and in five patients with glucose-6-phosphodehydrogenase (G6PD) deficiency without adverse reactions. (…)
008453, 07/26/2018	Succinylcholine	Anesthesiology	BCHE	Warnings, Precautions	**WARNINGS** (…) Succinylcholine is metabolized by plasma cholinesterase and should be used with caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene. **PRECAUTIONS** *Reduced Plasma Cholinesterase Activity* Succinylcholine should be used carefully in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. The likelihood of prolonged neuromuscular block following administration of succinylcholine must be considered in such patients (see DOSAGE AND ADMINISTRATION). Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for atypical plasma cholinesterase gene), pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. (…) (…) Patients homozygous for atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine. In these patients, a 5- to 10-mg test dose of succinylcholine may be administered to evaluate sensitivity to succinylcholine, or neuromuscular blockade may be produced by the cautious administration of a 1-mg/mL solution of succinylcholine by slow IV infusion. Apnea or prolonged muscle paralysis should be treated with controlled respiration.
017381, 08/01/2016	Sulfadiazine	Infectious Diseases	G6PD	Warnings	**WARNINGS** (…) The use of SILVADENE Cream 1% (silver sulfadiazine) in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur.
017377, 07/16/2014	Sulfamethoxazole and Trimethoprim (1)	Infectious Diseases	G6PD	Precautions	**PRECAUTIONS** Hemolysis In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see Clinical Pharmacology and Dosage and Administration).
017377, 07/16/2014	Sulfamethoxazole and Trimethoprim (2)	Infectious Diseases	Nonspecific (NAT)	Precautions	**PRECAUTIONS** *Electrolyte Abnormalities* (…) During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are “slow acetylators” may be more prone to idiosyncratic reactions to sulfonamides. (…)
007073, 03/04/2014	Sulfasalazine (1)	Gastroenterology	G6PD	Precautions	**PRECAUTIONS** *General* AZULFIDINE EN-tabs Tablets should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, AZULFIDINE EN-tabs should be discontinued immediately.
007073, 03/04/2014	Sulfasalazine (2)	Gastroenterology	Nonspecific (NAT)	Clincal Pharmacology	**CLINICAL PHARMACOLOGY** **Pharmacokinetics** *Metabolism*: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5- ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to 5-hydroxysulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a nonacetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible. **Special Populations** *Acetylator Status*: The metabolism of SP to AcSP is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life for SP (14.8 hours vs 10.4 hours) and an accumulation of higher plasma levels of SP than fast acetylators. The clinical implication of this is unclear;

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					however, in a small pharmacokinetic trial where acetylator status was determined, subjects who were slow acetylators of SP showed a higher incidence of adverse events.
211996, 05/03/2019	**Tafamidis**	Cardiology	TTR	Clinical Pharmacology, Clinical Studies	**12. CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** A proprietary TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer ex vivo. The TTR stabilization assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre- and post-treatment with 2-day in vitro denaturation with urea. Using this proprietary assay, a dose-dependent trend for greater TTR tetramer stabilization is observed for VYNDAQEL 80-mg compared to VYNDAQEL 20-mg. However, the clinical relevance of a higher TTR tetramer stabilization towards cardiovascular outcomes is not known. VYNDAQEL stabilized both the wild type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilized the TTR tetramer for 25 variants tested ex vivo. (…) **14 CLINICAL STUDIES** Efficacy was demonstrated in a multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (NCT01994889). Patients were randomized in a 1:2:2 ratio to receive VYNDAQEL 20 mg (n=88), VYNDAQEL 80 mg (administered as four 20-mg VYNDAQEL capsules) (n=176), or matching placebo (n=177) once daily for 30 months, in addition to standard of care (e.g., diuretics). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as baseline disease severity (NYHA Class). Transplant patients were excluded from this study. Table 1 describes the patient demographics and baseline characteristics. (See Tables 1 and 3, Figures 1 and 4)
210607, 08/08/2018	**Tafenoquine**	Infectious Diseases	G6PD	Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information	**2 DOSAGE AND ADMINISTRATION** **2.1 Tests to be Performed Prior to ARAKODA Dose Initiation** All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA [see Contraindications (4), Warnings and Precautions (5.1)]. **4 CONTRAINDICATIONS** ARAKODA is contraindicated in: • patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia [see Warnings and Precautions (5.2)]. • breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown [see Warnings and Precautions (5.3), Use in Specific Populations (8.2)]. **5 WARNINGS AND PRECAUTIONS** **5.1. Hemolytic Anemia** Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA [see Contraindications (4)]. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status [see Contraindications (4)]. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients [see Adverse Reactions (6.1)]. Monitor patients for clinical signs or symptoms of hemolysis [see Warnings and Precautions (5.6)]. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur. **5.2 G6PD Deficiency in Pregnancy and Lactation** **Potential Harm to the Fetus** The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Use in Specific Populations (8.1 and 8.3)]. **Potential Harm to the Breastfeeding Infant** A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown [see Contraindications (4)]. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose [see Use in Specific Populations (8.2)]. **8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy Risk Summary**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PDdeficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy [see Warnings and Precautions (5.2)]. (…) **8.2 Lactation Risk Summary** A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown [see Contraindications (4) and Clinical Considerations]. There is no information regarding the presence of ARAKODA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition. **Clinical Considerations** Check the infant's G6PD status before maternal breastfeeding commences. If an infant is G6PDdeficient, exposure to ARAKODA during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency or whose G6PD status is unknown, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose of ARAKODA. **8.3 Females and Males of Reproductive Potential** **Contraception** ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus [see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA. **17 PATIENT COUNSELING INFORMATION** **G6PD Testing and Hemolytic Anemia** Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia [see Warnings and Precautions (5.1)]. **Lactation** Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose [see Contraindication (4), Warnings and Precautions (5.2), Use in Specific Populations (8.2)].
211651, 10/16/2018	Talazoparib (1)	Oncology	BRCA	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA [see Dosage and Administration (2.1)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients for the treatment of advanced breast cancer with TALZENNA based on the presence of germline BRCA mutations [see Indications and Usage (1), Clinical Studies (14)]. Information on the FDA-approved test for the detection of BRCA mutations is available at http://www.fda.gov/companiondiagnostics. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Treatment of gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer *EMBRACA* The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (n=286) or a chemotherapy agent (capecitabine, eribulin, gemcitabine, or vinorelbine) of the healthcare provider's choice (n=126) until disease progression or unacceptable toxicity. (…) **14 CLINICAL STUDIES** **EMBRACA Study (NCT01945775)** Deleterious or Suspected Deleterious Germline BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive TALZENNA 1 mg or healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system (CNS) metastasis (yes versus no). (…) (…) No prior treatment with a PARP inhibitor was permitted. Of the 431 patients randomized in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious gBRCAm using a clinical trial assay; out of which 354 (82%) were confirmed using the BRACAnalysis CDx®. BRCA mutation status (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms. (…)
211651, 10/16/2018	Talazoparib (2)	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse	**1 INDICATIONS AND USAGE**

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Reactions, Clinical Studies	TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA [see Dosage and Administration (2.1)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Treatment of gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer *EMBRACA* The safety of TALZENNA as monotherapy was evaluated in gBRCAm patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (n=286) or a chemotherapy agent (capecitabine, eribulin, gemcitabine, or vinorelbine) of the healthcare provider's choice (n=126) until disease progression or unacceptable toxicity. (…) **14 CLINICAL STUDIES** **EMBRACA Study (NCT01945775)** Deleterious or Suspected Deleterious Germline BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive TALZENNA 1 mg or healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system (CNS) metastasis (yes versus no). (…)
021807, 04/08/2019	Tamoxifen (1)	Oncology	ESR, PGR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Metastatic Breast Cancer** SOLTAMOX is indicated for the treatment of adult patients with estrogen receptor-positive metastatic breast cancer. **1.2 Adjuvant Treatment of Breast Cancer** SOLTAMOX is indicated: • for the adjuvant treatment of adult patients with early stage estrogen receptor-positive breast cancer • to reduce the occurrence of contralateral breast cancer in adult patients when used as adjuvant therapy for the treatment of breast cancer. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Anastrozole Adjuvant Trial (ATAC: Arimidex, Tamoxifen, Alone or in Combination) – Study of Anastrozole Compared to Tamoxifen for Adjuvant Treatment of Early Breast Cancer* At a median follow-up of 33 months, the combination of anastrozole and tamoxifen did not demonstrate an efficacy benefit when compared to tamoxifen monotherapy in all patients as well as in the hormone receptorpositive subpopulation. The combination treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving anastrozole 1 mg and tamoxifen 20 mg monotherapy, respectively. (…) **12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women's Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p<0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers. **14 CLINICAL STUDIES** **14.2 Adjuvant Treatment of Breast Cancer** Pooled Studies of Adjuvant Treatment of Breast Cancer The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, 1995, 1998 and 2011. The 10-year outcome data were reported in 1998 for 36,689 women in 55 randomized trials of another formulation of adjuvant tamoxifen using doses of 20 to 40 mg per day for 1 to 5+ years. Twenty-five percent of patients received 1 year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Fortyeight percent of tumors were estrogen receptor (ER)- positive (>10 fmol/mg), 21% were ER-poor (<10 fmol/mg), and 31% were ER-unknown. Among 29,441 patients with ER-positive or ER-unknown breast cancer, 58% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node-positive disease and 46% had node-negative disease. *In women with ER-positive or ER-unknown breast cancer:* • With positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for tamoxifen vs. 50.5% for control (log-rank 2p <0.00001). The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (log-rank 2p <0.00001).

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Last Updated: 06/2019

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					• With negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (log-rank 2p <0.00001). The recurrence-free rate at 10 years was 79.2% for tamoxifen vs. 64.3% for control (log-rank 2p <0.00001). • Who received 1 year or less, 2 years, or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17%, and 26%, respectively (2p <0.003). The corresponding reductions in breast cancer recurrence were 21%, 29%, and 47% (2p <0.00001). Results in patients with ER-poor breast cancer • Benefit is less clear for women with ER-poor breast cancer in whom the proportional reduction in recurrence was 10% (2p = 0.007) for all durations taken together, or 9% (2p = 0.02) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (not significant). Node-positive: Individual Studies (…) In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50 to 59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while survival results were poorer in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60 to 70 years, there was an improvement in disease-free survival with tamoxifen without any clear relationship to estrogen or progesterone receptor status. (…) Node–negative: Individual Studies NSABP B-14, a prospective, double-blind, randomized study, compared another formulation of tamoxifen to placebo as adjuvant therapy in women with axillary node-negative, estrogen-receptor positive (≥10 fmol/mg cytosol protein) breast cancer (following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50. One additional randomized study (NATO) demonstrated improved disease-free survival for another formulation of tamoxifen compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of tamoxifen appeared to be independent of estrogen receptor status. Anastrozole Adjuvant Trial (ATAC: Arimidex, Tamoxifen, Alone or in Combination) – Study of Anastrozole Compared to Tamoxifen for Adjuvant Treatment of Early Breast Cancer A trial was conducted in 9,366 postmenopausal women with operable breast cancer who were randomized to receive adjuvant treatment with either anastrozole 1 mg daily, another formulation of tamoxifen 20 mg daily, or a combination of these two treatments for 5 years or until recurrence of the disease. At a median follow-up of 33 months, the combination of anastrozole and tamoxifen did not demonstrate any efficacy benefit when compared to tamoxifen alone in all patients, as well as in the hormone receptor-positive subpopulation. The combination treatment arm was discontinued from the trial [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. Refer to the full prescribing information for anastrozole tablets for additional information on this trial. (…) **14.4 Reduction in Breast Cancer Incidence in Women at High Risk** Breast Cancer Prevention Trial (NSABP P-1) (…) Table 9 describes the characteristics of the breast cancers in the NSABP P-1 trial in women at high risk for breast cancer. Tamoxifen decreased the incidence of small estrogen receptor-positive tumors, but did not alter the incidence of estrogen receptor-negative tumors or larger tumors. (See Table 9) (…)
021807, 04/08/2019	**Tamoxifen (2)**	Oncology	F5 (Factor V Leiden)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.2 Thromboembolic Events** (…) In a small substudy (N = 81) of the NSABP-1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations G20210A as a means to identify those who may not be appropriate candidates for tamoxifen therapy. (…)
021807, 04/08/2019	**Tamoxifen (3)**	Oncology	F2 (Prothrombin)	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.2 Thromboembolic Events** (…) In a small substudy (N = 81) of the NSABP-1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations G20210A as a means to identify those who may not be appropriate candidates for tamoxifen therapy. (…)
021807, 04/08/2019	**Tamoxifen (4)**	Oncology	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Metabolism Tamoxifen is extensively metabolized by CYP450 enzymes, including CYP3A, CYP2D6, CYP2C9, CYP2C19, and CYP2B6. N-desmethyltamoxifen, formed predominantly by CYP3A, is the major metabolite found in plasma. The pharmacological activity of N-desmethyltamoxifen is similar to that of tamoxifen. Endoxifen and 4-hydroxytamoxifen, identified as minor metabolites, have 100-fold greater affinity for the estrogen receptor and 30 to 100-fold greater potency in suppressing estrogen-dependent cell proliferation than tamoxifen. The polymorphic enzyme CYP2D6 is involved in the formation of endoxifen and 4-hydroxytamoxifen, and it is the key enzyme that catalyzes the formation of endoxifen from N-desmethyltamoxifen. Endoxifen concentrations may differ among patients because of various CYP2D6 genotypes [see Clinical Pharmacology (12.5)]. Phase 2 enzymes, such as SULT1A1, UGT2B7, and UGT1A4, are associated with tamoxifen clearance from plasma. Drug-Drug Interactions *CYP2D6 Inhibitors* CYP2D6 Inhibitors Although concomitant administration of CYP2D6 inhibitors reduces the plasma concentration of endoxifen, a potent metabolite, the clinical significance is not well established [see Drug Interactions (7.4)]. The mean steady-state endoxifen plasma concentration in patients taking CYP2D6 inhibitors was significantly reduced compared to those not taking concomitant CYP2D6 inhibitors (14.8 ± 10.6 versus 26.7 ± 15.4 ng/mL). The mean steady-state plasma concentration of endoxifen in CYP2D6 normal metabolizers who were not receiving CYP2D6 inhibitors was 31.4 ± 14.7 ng/mL compared to 8.8 ± 3.5 ng/mL in CYP2D6 normal metabolizers receiving potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) with tamoxifen. The plasma levels of endoxifen in CYP2D6 normal metabolizers taking potent CYP2D6 inhibitors were similar to the levels observed in CYP2D6 poor metabolizers taking no CYP2D6 inhibitors (8.8 versus 7.2 ng/mL). **12.5 Pharmacogenomics**

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Last Updated: 06/2019

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					The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established. CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6. In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women's Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers (p<0.0001), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.
020579, 01/23/2019	**Tamsulosin**	Urology	CYP2D6	Warnings and Precautions, Adverse Interactions, Clinical Pharmacology	**5 WARNINGS AND PRECAUTIONS** **5.2 Drug Interactions** Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6. FLOMAX capsules 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. FLOMAX capsules should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terbinafine) inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers particularly at a dose higher than 0.4 mg (e.g., 0.8 mg) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. (…) **7 DRUG INTERACTIONS** **7.1 Cytochrome P450 Inhibition Strong and Moderate Inhibitors of CYP3A4 or CYP2D6** (…) Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when FLOMAX 0.4 mg is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, FLOMAX 0.4 mg capsules should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]. (…) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** **Drug Interactions** **Cytochrome P450 Inhibition** **Strong and Moderate Inhibitors of CYP3A4 or CYP2D6** (…) The effects of paroxetine (a strong inhibitor of CYP2D6) at 20 mg once daily for 9 days on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range 23 to 47 years). Concomitant treatment with paroxetine resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively [see Warnings and Precautions (5.2) and Drug Interactions (7.1)]. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). A fraction of the population (about 7% of Caucasians and 2% of African Americans) are CYP2D6 PMs. Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when FLOMAX 0.4 mg is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, FLOMAX 0.4 mg capsules should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) [see Warnings and Precautions (5.2) and Drug Interactions (7.1)]. (…)
201917, 10/28/2013	**Telaprevir**	Infectious Diseases	IFNL3 (IL28B)	Clinical Pharmacology, Clinical Studies	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenomics** A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR). rs12979860 was genotyped in 454 of 1088 subjects in Trial 108 (treatment-naïve) and 527 of 662 subjects in Trial C216 (previously treated) [see Clinical Studies (14.2 and 14.3) for trial descriptions]. SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naïve subjects receiving PR48 (Table 9). Among both treatment-naïve and previous treatment failures, subjects of all IL28B genotypes appeared to have higher SVR rates with regimens containing 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 subtrial population relative to the overall trial population. In Trial C211, all subjects were prospectively tested for IL28B variants; there were no clinically relevant differences in SVR12 responses between q8h and twice-daily dosing within the genetic subgroups. (See Table 9) **14 CLINICAL STUDIES** **14.2 Treatment-Naïve Adults** *Trial C211 (OPTIMIZE)* (…) SVR rates were similar for the T12 (twice daily)/PR and T12 (q8h)/PR groups across subgroups determined by sex, age, race, ethnicity, body mass index, HCV genotype subtype, IL28B genotype, baseline HCV RNA (less than 800,000, greater than or equal to 800,000 IU per mL), and extent of liver fibrosis. However, there were small numbers of subjects enrolled in some key subgroups. (…)
021894, 09/13/2017	**Tetrabenazine**	Neurology	CYP2D6	Dosage and Administration, Warnings and Precautions, Use in Specific Populations,	**2 DOSAGE AND ADMINISTRATION** **2.2 Individualization of Dose** Dosing Recommendations Above 50 mg per day Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. *Extensive and Intermediate CYP2D6 Metabolizers*

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
				Clinical Pharmacology	Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a 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., antidepressants) [see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. *Poor CYP2D6 Metabolizers* In PMs, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. **5 WARNINGS AND PRECAUTIONS** **5.3 Laboratory Tests** Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are poor metabolizers (PMs), extensive (EMs) or intermediate metabolizers (IMs) of XENAZINE. Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient's CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg [see Dosage and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. **8 USE IN SPECIFIC POPULATIONS** **8.7 Poor or Extensive CYP2D6 Metabolizers** Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]. *Poor Metabolizers* Poor CYP2D6 metabolizers (PM) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) compared to EMs. The dosage should, therefore, be adjusted according to a patient's CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]. *Extensive / Intermediate Metabolizers* In extensive (EMs) or intermediate metabolizers (IMs), the dosage of XENAZINE can be titrated to a maximum single dose of 37.5 mg and a recommended maximum daily dose of 100 mg [see Dosage and Administration (2.2), Drug Interactions (7.1), Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Specific Populations* *Poor CYP2D6 Metabolizers* Although the pharmacokinetics of XENAZINE and its metabolites in patients who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively) [see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.7)].
012429, 05/23/2018	Thioguanine (1)	Oncology	TPMT	Dosage and Administration, Warnings, Precautions, Clinical Pharmacology	**DOSAGE AND ADMINISTRATION** (…) Patients with homozygous deficiency of either TPMT or NUDT15 enzyme typically require 10% or less of the standard thioguanine dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. Reduce the dosage based on tolerability. **WARNINGS** **(…)** Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine. **PRECAUTIONS** *Laboratory Tests* Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression. (see WARNINGS). **CLINICAL PHARMACOLOGY**

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Last Updated: 06/2019

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					Metabolism and Genetic Polymorphism Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-offunction alleles of the TPMT gene and have little or no TMPT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common lossof-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient's actual TPMT activity.
012429, 05/23/2018	**Thioguanine (2)**	Oncology	NUDT15	Dosage and Administration, Warnings, Precautions, Clinical Pharmacology	**DOSAGE AND ADMINISTRATION** (…) Patients with homozygous deficiency of either TPMT or NUDT15 enzyme typically require 10% or less of the standard thioguanine dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. Reduce the dosage based on tolerability. **WARNINGS** **(…)** Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine. **PRECAUTIONS** *Laboratory Tests* Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression. (see WARNINGS). **CLINICAL PHARMACOLOGY** *Metabolism and Genetic Polymorphism* Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%. Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-offunction alleles of the TPMT gene and have little or no TMPT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common lossof-function NUDT15 alleles have been observed. Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient's actual TPMT activity.
011808	**Thioridazine**	Psychiatry	CYP2D6	Contraindications, Warnings, Precautions	Labeling not electronically available on Drugs@FDA
022433, 04/03/2019	**Ticagrelor**	Cardiology	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.5 Pharmacogenetics** In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status.
207981, 02/22/2019	**Tipiracil and Trifluridine (1)**	Oncology	ERBB2 (HER2)	Clinical Studies	**14 CLINICAL STUDIES** **14.2** Metastatic Gastric Cancer

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					(…) All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%, positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy. (…)
207981, 02/22/2019	**Tipiracil and Trifluridine (2)**	Oncology	RAS	Clinical Studies	**14 CLINICAL STUDIES** **14.1** Metastatic Colorectal Cancer (…) Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months) and region (Japan vs. US, Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS). A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab. (See Table 7)
018894	**Tolazamide**	Endocrinology	G6PD	Precautions	Labeling not electronically available on Drugs@FDA
010670	**Tolbutamide**	Endocrinology	G6PD	Precautions	Labeling not electronically available on Drugs@FDA
021228, 07/13/2018	**Tolterodine**	Urology	CYP2D6	Warnings and Precautions, Drug Interactions, Clinical Pharmacology	**5 WARNINGS AND PRECAUTIONS** **5.9 Use in Patients with Congenital or Acquired QT Prolongation** In a study of the effect of tolterodine immediate release tablets on the QT interval [see CLINICAL PHARMACOLOGY (12.2)], the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. (…) **7 DRUG INTERACTIONS** **7.1 Potent CYP2D6 Inhibitors** Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine [see CLINICAL PHARMACOLOGY (12.1)]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [see CLINICAL PHARMACOLOGY (12.3)]. **7.2 Potent CYP3A4 Inhibitors** Ketoconazole (200 mg daily), a potent CYP3A4 inhibitor, increased the mean Cmax and AUC of tolterodine by 2- and 2.5-fold, respectively, in CYP2D6 poor metabolizers. For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, clarithromycin, or ritonavir, the recommended dose of DETROL LA is 2 mg once daily [see DOSAGE AND ADMINISTRATION(2.2) and CLINICAL PHARMACOLOGY (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The effect of 2 mg BID and 4 mg BID of DETROL immediate release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18–55 years. Study subjects [approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs)] completed sequential 4-day periods of dosing with moxifloxacin 400 mg QD, tolterodine 2 mg BID, tolterodine 4 mg BID, and placebo. The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon coadministration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers [see DRUG INTERACTIONS (7.2)]. QT interval was measured over a 12-hour period following dosing, including the time of peak plasma concentration (Tmax) of tolterodine and at steady state (Day 4 of dosing). (…) (…) Tolterodine's effect on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QTc interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study. (…) **12.3 Pharmacokinetics** *Variability in Metabolism:* A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6, the enzyme responsible for the formation of 5-HMT from tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers." Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HMT. *Excretion:* Following administration of a 5 mg oral dose of 14C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (< 2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as 5-HMT.

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

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					A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine extended release and 5 HMT in extensive (EM) and poor (PM) metabolizers is provided in Table 3. These data were obtained following single and multiple doses of tolterodine extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM). (See Table 3) (…) *Drug Interactions:* Potent CYP2D6 inhibitors: Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate release in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT, the pharmacologically active metabolite of tolterodine). Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be CYP2D6 extensive metabolizers of tolterodine immediate release to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate release and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered. Potent CYP3A4 inhibitors: The effect of a 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were CYP2D6 poor metabolizers. In the presence of ketoconazole, the mean Cmax and AUC of tolterodine increased by 2- and 2.5 fold, respectively. Based on these findings, other potent CYP3A4 inhibitors may also lead to increases of tolterodine plasma concentrations. (…)
020497, 05/12/2017	**Toremifene**	Oncology	ESR (Hormone Receptor)	Indications and Usage, Clinical Studies	**1 INDICATIONS AND USAGE** FARESTON® is an estrogen agonist/antagonist indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors. **14 CLINICAL STUDIES** Three prospective, randomized, controlled clinical studies (North American, Eastern European, and Nordic) were conducted to evaluate the efficacy of FARESTON for the treatment of breast cancer in postmenopausal women. The patients were randomized to parallel groups receiving FARESTON 60 mg (FAR60) or tamoxifen 20 mg (TAM20) in the North American Study or tamoxifen 40 mg (TAM40) in the Eastern European and Nordic studies. The North American and Eastern European studies also included high-dose toremifene arms of 200 and 240 mg daily, respectively. The studies included postmenopausal patients with estrogen-receptor (ER) positive or estrogenreceptor (ER) unknown metastatic breast cancer. (…)
020281, 04/08/2019	**Tramadol**	Anesthesiology	CYP2D6	Boxed Warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Patient Counseling Information	**BOXED WARNING** **ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN** Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in a t l e a s t one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (see WARNINGS). ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol (see WARNINGS). **5 WARNINGS AND PRECAUTIONS** **5.4 Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Lifethreatening Respiratory Depression in Children** Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon post-marketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death: • ULTRAM is contraindicated for all children younger than 12 years of age [see Contraindications (4)]. • ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. • Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. • As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose [see Use in Specific Populations (8.4), Overdosage (10)]. *Nursing Mothers* Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultrarapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking ULTRAM could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with ULTRAM [see Use in Specific Populations (8.2)]. *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

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra- rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdosage (10)]. Therefore, individuals who are ultra-rapid metabolizers should not use ULTRAM. **8 USE IN SPECIFIC POPULATIONS** **8.2 Lactation** **Risk Summary** ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Tramadol and its metabolite, O-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding [see Clinical Pharmacology (12)]. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ULTRAM [see Warnings and Precautions (5.4)]. (…) **8.4 Pediatric Use** The safety and effectiveness of ULTRAM in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol [see Warnings and Precautions (5.4)]. In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death: • ULTRAM is contraindicated for all children younger than 12 years of age [see Contraindications (4)]. • ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* (…) Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower. (…) *Poor / Extensive Metabolizers, CYP2D6* The formation of the active metabolite, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower. **17 PATIENT COUNSELING INFORMATION** Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children Advise caregivers that ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 years of age receiving ULTRAM to monitor for signs of respiratory depression [see Warnings and Precautions (5.4)].
204114, 05/04/2018	**Trametinib (1)**	Oncology	BRAF	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information	**1 INDICATIONS AND USAGE** **1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma** MEKINIST® is indicated, as a single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.2)]. **1.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma** MEKINIST is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see Dosage and Administration (2.1), (2.3)]. **1.3 BRAF V600E Mutation-Positive Metastatic NSCLC** MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see Dosage and Administration (2.1), (2.4)]. **1.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer**

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

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					MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options [see Dosage and Administration (2.1), (2.5)]. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Melanoma • Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.1), (14.2)]. • Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics. NSCLC • Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.3)]. • Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics. ATC • Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see Clinical Studies (14.4)]. **6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *Unresectable or Metastatic BRAF V600E Mutation Positive Melanoma* *MEKINIST Administered as a Single Agent* Table 3 presents adverse reactions identified from analyses of the METRIC study, a randomized, open-label trial of patients with BRAF V600E or V600K mutation-positive melanoma receiving MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine 1,000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 every 3 weeks) [see Clinical Studies (14.1)]. (…) *MEKINIST Administered with Dabrafenib* The safety of MEKINIST, administered with dabrafenib, was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma who received MEKINIST in two trials, the COMBI-d study (n = 209), a multicenter, double-blind, randomized (1:1), active-controlled trial and the COMBI-v study (n = 350), a multicenter, open-label, randomized (1:1), active-controlled trial. (…) *Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma* The safety of MEKINIST when administered with dabrafenib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study [see Clinical Studies (14.2)]. (…) *Metastatic, BRAF V600E Mutation-Positive NSCLC* The safety of MEKINIST when administered with dabrafenib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928). (…) (…) *Locally Advanced or Metastatic, BRAF V600E-Mutation Positive, Anaplastic Thyroid Cancer (ATC)* The safety of MEKINIST when administered with dabrafenib was evaluated in a nine-cohort, multicenter, nonrandomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). (…) **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** Administration of 1 mg and 2 mg MEKINIST to patients with BRAF V600 mutation-positive melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis). **12.3 Pharmacokinetics** The pharmacokinetics (PK) of trametinib were characterized following single- and repeat-oral administration in patients with solid tumors and BRAF V600 mutation-positive metastatic melanoma. (…) **14 CLINICAL STUDIES** **14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma** *Mekinist as a Single Agent* The safety and efficacy of MEKINIST were evaluated in an international, multicenter, randomized (2:1), open-label, active-controlled trial (Trial 1) in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. (…) (…) Tumor tissue was evaluated for BRAF mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients (196 patients treated with MEKINIST and 93 chemotherapy-treated patients) were also tested retrospectively using an FDA-approved companion diagnostic test, THxID™-BRAF assay. (…) (…) The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (less than 1%). The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for patients treated with MEKINIST and 3.1 months for patients treated with chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST. (…) *Mekinist with Dabrafenib* The safety and efficacy of MEKINIST administered with dabrafenib were evaluated in an international, randomized, double-blind, active-controlled trial (the COMBI-d study; NCT01584648). The COMBI-d study compared dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					MEKINIST 2 mg once daily plus dabrafenib 150 mg twice daily or dabrafenib 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (greater than the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR). In the COMBI-d study, 423 patients were randomized to MEKINIST plus dabrafenib (n = 211) or dabrafenib plus placebo (n = 212). The median age was 56 years (range: 22 to 89 years), 53% were male, >99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIc, 66% had M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing with the FDA-approved companion diagnostic test; 85% had BRAF V600E mutation-positive melanoma and 15% had BRAF V600K mutation-positive melanoma. **14.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma** COMBI-AD (NCT01682083) was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations as detected by the THxID™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive MEKINIST 2 mg once daily in combination with dabrafenib 150 mg twice daily or two placebos for up to 1 year. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable intransit metastases, distant metastatic disease, or prior systemic anticancer treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIIa, IIIb, or IIIc). (…) In COMBI-AD, a total of 870 patients were randomized: 438 to the MEKINIST in combination with dabrafenib and 432 to placebo. Median age was 51 years (range: 18 to 89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years. (See Table 13) (…) **14.3 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, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). (…) In a subgroup analysis of patients with retrospectively centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 14. **14.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer (ATC)** The safety and efficacy of MEKINIST administered with dabrafenib was evaluated in Study BRF117019 (NCT02034110), an activity-estimating, nine-cohort, multi-center, non-randomized, open-label trial in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. (…) **14.3 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, 98% had baseline ECOG PS of 0 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No patient achieved a confirmed partial or complete response as determined by the clinical investigators. **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)].
204114, 05/04/2018	Trametinib (2)	Oncology	G6PD	Adverse Reactions	**6 ADVERSE REACTIONS** **6.1 Clinical Trials Experience** *MEKINIST Administered with Dabrafenib* (…) The trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVO or RPED, QTcB interval ≥480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency. (…)
204114, 05/04/2018	Trametinib (3)	Oncology	RAS	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **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% (1/93) 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)].

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

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103792, 11/29/2018	Trastuzumab (1)	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Adjuvant Breast Cancer** Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel • with docetaxel and carboplatin • as a single agent following multi-modality anthracycline based therapy. **1.2 Metastatic Breast Cancer** Herceptin is indicated: • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. **1.3 Metastatic Gastric Cancer** Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics. Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamics** *Cardiac Electrophysiology* The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors. **14 CLINICAL STUDIES** **14.1 Adjuvant Breast Cancer** The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4). *Studies 1 and 2* In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). (…) *Study 3* In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. (…) (…) Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). (…) *Study 4* In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. (…) (…) Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 10. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups. (See Table 10) (…) **14.2 Metastatic Breast Cancer** The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic

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Blue text represents the most recent addtions and/or changes since last posted version.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					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)
103792, 11/29/2018	Trastuzumab (2)	Oncology	ESR, PGR (Hormone Receptor)	Clinical Studies	**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 PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80). (See Table 9) (…)
020438, 07/01/2008	Tretinoin	Oncology	PML-RARA	Indications and Usage, Warnings, Clinical Pharmacology	**INDICATIONS AND USAGE** VESANOID (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. VESANOID is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with VESANOID. **WARNINGS** *Patients Without the t(15;17) Translocation* Initiation of therapy with VESANOID may be based on the morphological diagnosis of acute promyelocytic leukemia. Confirmation of the diagnosis of APL should be sought by detection of the t(15;17) genetic marker by cytogenetic studies. If these are negative, PML/RARα fusion should be sought using molecular diagnostic techniques. The response rate of other AML subtypes to VESANOID has not been demonstrated; therefore, patients who lack the genetic marker should be considered for alternative treatment. **CLINICAL PHARMACOLOGY** (…) Responses were seen in 3 of 4 patients for whom cytogenetic analysis failed to detect the t(15;17) translocation typically seen in APL. The t(15;17) translocation results in the PML/RARα gene, which appears necessary for this disease. Molecular genetic studies were not conducted in these cases, but it is likely they represent cases with a masked translocation giving rise to PML/RARα. Responses to tretinoin have not been observed in cases in which PML/RARα fusion has been shown to be absent.
016792, 07/17/2014	Trimipramine	Psychiatry	CYP2D6	Precautions	**PRECAUTIONS** *Drugs Metabolized by P450 2D6* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among 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, 06/06/2019	Umeclidinium	Pulmonary	CYP2D6	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics**

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					Umeclidinium and Cytochrome P450 2D6: In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing to normal (ultrarapid, extensive, and intermediate metabolizers) and CYP2D6 poor metabolizer subjects (Figure 1).
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, 08/10/2018	Valbenazine	Neurology	CYP2D6	Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.3 Dosage Recommendations for Known CYP2D6 Poor Metabolizers** Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]. **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. (…) **8 USE IN SPECIFIC POPULATIONS** **8.6 CYP2D6 Poor Metabolizers** Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers [see Dosage and Administration (2.2)]. Increased exposure (Cmax and AUC) to valbenazine's active metabolite is anticipated in CYP2D6 poor metabolizers. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions [see Clinical Pharmacology (12.3)]. **12 CLINICAL PHARMACOLOGY** **12.2 Pharmacodynamic** *Cardiac Electrophysiology* (…) INGREZZA may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking an INGREZZA 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean QT prolongation of 11.7 msec (14.7 msec upper bound of double-sided 90% CI) as compared to otherwise healthy volunteers given INGREZZA, who had a mean QT prolongation of 6.7 msec (8.4 msec) [see Warnings and Precautions (5.2)].
018081, 02/21/2019	Valproic Acid (1)	Neurology	POLG	Boxed Warning, Contraindications, Warnings and Precautions	**BOXED WARNING** WARNING: LIFE THREATENING ADVERSE REACTIONS *Patients with Mitochondrial Disease* There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g., Alpers Huttenlocher Syndrome). Depakene is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder [see Contraindications (4)]. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice [see Warnings and Precautions (5.1)]. **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 POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder [see Contraindications (4)]. Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene for the development of acute liver injury with regular clinical assessments and serum liver 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)].
018081, 02/21/2019	Valproic Acid (2)	Neurology	Nonspecific (Urea Cycle Disorders)	Contraindications, Warnings and Precautions	**4 CONTRAINDICATIONS** (…) Depakene is contraindicated in patients with known urea cycle disorders [see Warnings and Precautions (5.6)]. **5 WARNINGS AND PRECAUTIONS** **5.6 Urea Cycle Disorders (UCD)** Valproic acid is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders [see Contraindications (4) and Warnings and Precautions (5.10)]. **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 (5.11)]. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders [see Contraindications (4) and Warnings and Precautions (5.6, 5.10)]. 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.
202429, 11/06/2017	Vemurafenib (1)	Oncology	BRAF	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reasctions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies, Patient Counseling Information	**1 INDICATIONS AND USAGE** **1.1 Unresectable or Metastatic Melanoma** ZELBORAF® is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Limitation of Use: ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)]. **1.2 Erdheim-Chester Disease** ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. **2 DOSAGE AND ADMINISTRATION** **2.1 Patient Selection** Confirm the presence of BRAF V600E mutation in melanoma tumor specimens prior to initiation of treatment with ZELBORAF [see Warnings and Precautions (5.2)]. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at http://www.fda.gov/CompanionDiagnostics. **5 WARNINGS AND PRECAUTIONS** **5.1 New Primary Malignancies** *(…) Other Malignancies* Based on mechanism of action, ZELBORAF may promote malignancies associated with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies. **5.2 Tumor Promotion in BRAF Wild-Type Melanoma** In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation in tumor specimens prior to initiation of ZELBORAF [see Indications and Usage (1) and Dosage and Administration (2.1)]. **5.5 QT Prolongation** Concentration-dependent QT prolongation occurred in an uncontrolled, open-label QT sub-study in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [see Clinical Pharmacology (12.2)]. (…)

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Last Updated: 06/2019

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					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 V600 mutation-positive ECD received ZELBORAF 960 mg twice daily. The median treatment duration for ECD patients in this study was 14.2 months. Table 3 presents adverse reactions reported in at least 20% of BRAF V600 mutation-positive ECD patients treated with ZELBORAF. In Trial 4, the most commonly reported adverse reactions (> 50%) in patients with BRAF V600 mutationpositive 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 V600E mutation-positive metastatic melanoma, patients administered vemurafenib 960 mg orally twice daily did not experience large changes in mean QTc interval (i.e., > 20 ms) from baseline. (…) **12.3 Pharmacokinetics** The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of 960 mg twice daily with dosing approximately 12 hours apart. The population pharmacokinetic analysis pooled data from 458 patients. At steady-state, vemurafenib exhibits linear pharmacokinetics within the 240 mg to 960 mg dose range. **14 CLINICAL STUDIES** *Treatment-Naïve Patients with BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma* Trial 1, an international, open-label, randomized controlled trial, equally allocated 675 patients with treatment-naive, BRAF V600E mutation-positive unresectable or metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, to receive ZELBORAF 960 mg by mouth twice daily (n=337) or dacarbazine 1000 mg/m^2 intravenously on Day 1 every 3 weeks (n=338). (See Table 5) (…) *Patients with BRAF V600E Mutation-Positive Metastatic Melanoma Who Received Prior Systemic Therapy* (…) In a single-arm, multicenter, multinational trial (Trial 2), 132 patients with BRAF V600E mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, who had received at least one prior systemic therapy, received ZELBORAF 960 mg by mouth twice daily.. (…) *Patients with BRAF V600E Mutation-Positive Melanoma with Brain Metastases* The activity of ZELBORAF for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in an open-label, multicenter, single-arm, two cohort trial (Trial 3). (See Table 6)(…) *Patients with Wild-Type BRAF Melanoma* ZELBORAF has not been studied in patients with wild-type BRAF melanoma [see Warnings and Precautions (5.2)]. *Patients with Erdheim-Chester Disease (ECD)* An open-label, multicenter, single-arm, multiple cohort study of ZELBORAF (Trial 4) was conducted in patients ≥ 16 years of age with non-melanoma BRAF V600 mutation–positive diseases. (…) **17 PATIENT COUNSELING INFORMATION** Healthcare providers should advise patients of the potential benefits and risks of ZELBORAF and instruct their patients to read the Medication Guide before starting ZELBORAF therapy. Inform patients of the following: • Evidence of BRAF V600E mutation in the tumor specimen with an FDA approved test is necessary to identify patients for whom treatment with ZELBORAF is indicated [see Dosage and Administration (2.1)]. (…)
202429, 11/06/2017	Vemurafenib (2)	Oncology	RAS	Warnings and Precautions, Adverse Reactions	**5 WARNINGS AND PRECAUTIONS** *Other Malignancies* Based on mechanism of action, ZELBORAF may promote malignancies associated with activation of RAS through mutation or other mechanisms [see Warnings and Precautions (5.2)]. Monitor patients receiving ZELBORAF closely for signs or symptoms of other malignancies. **6 ADVERSE REACTIONS** **6.2 Postmarketing Experience** The following adverse reactions have been identified during post approval use of ZELBORAF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Neoplasms benign, malignant and unspecified (incl. cysts and polyps)*

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					Progression of pre-existing chronic myelomonocytic leukemia with NRAS mutation [see Warnings and Precautions (5.1)]. (…)
020699, 12/19/2017	Venlafaxine	Psychiatry	CYP2D6	Drug Interactions, Use in Specific Populations, Clinical Pharmacology	**7 DRUG INTERACTIONS** **7.5 Weight Loss Agents** The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. (See Figure 1) **8 USE IN SPECIFIC POPULATIONS** **8.6 Age and Gender** A population pharmacokinetic analysis of 404 Effexor-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary [see Dosage and Administration (2.6)] (see Table 15). (See Figure 3) **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** **Metabolism and elimination** Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels (poor metabolizers) had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 levels (extensive metabolizers) [see Use in Specific Populations 8.7].
208573, 05/15/2019	Venetoclax (1)	Oncology	Chromosome 17p	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma** Combination Therapy MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (See Table 21) (…) Monotherapy The efficacy of VENCLEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies. Study M13-982 The efficacy of VENCLEXTA was established in study M13-982 (NCT01889186), an openlabel, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. (See Table 23) (…) Study M12-175 Study M12-175 (NCT01328626) was a multicenter, open-label trial that enrolled previously treated patients with CLL or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients (59 with CLL, 8 with SLL) who had received a 400 mg daily dose of VENCLEXTA. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months). The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% of patients had ALC ≥25 x 109 /L, 33% had documented unmutated IgVH, and 21% had documented 17p deletion. (…) Study M14-032 Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≥5 cm, 31% had an absolute lymphocyte count ≥25 x 109 /L, 57% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)
208573, 05/15/2019	Venetoclax (2)	Oncology	Chromosome 11q	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma** Combination Therapy CCL14 (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…) MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…)
208573, 05/15/2019	Venetoclax (3)	Oncology	TP53	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma** Combination Therapy CCL14

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					(…) The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLcr<70 mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmutated IgVH in 57%. (…) MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (See Table 17) (…) **14.2 Acute Myeloid Leukemia** Study M14-358 VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Study M14-387 (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)
208573, 05/15/2019	Venetoclax (4)	Oncology	IDH1	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Acute Myeloid Leukemia** Study M14-358 VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Study M14-387 (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)
208573, 05/15/2019	Venetoclax (5)	Oncology	IDH2	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Acute Myeloid Leukemia** Study M14-358 VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Study M14-387 (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)
208573, 05/15/2019	Venetoclax (6)	Oncology	IGH	Clinical Studies	**14 CLINICAL STUDIES** **14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma** Combination Therapy CCL14 (…) The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLcr<70mL/min. A 17p deletion was detected in 8% of patients, TP53 mutations in 7%, 11q deletion in 19%, and unmutated IgVH in 57%. (…) MURANO (…) Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, TP53 mutations in 25%, 11q deletion in 32%, and unmutated IgVH in 63%. (…) Study M12-175 (…) The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% of patients had ALC ≥25 x 109 /L, 33% had documented unmutated IgVH, and 21% had documented 17p deletion. (…) Study M14-032 (…) Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≥5 cm, 31% had an absolute lymphocyte count ≥25 x 109 /L, 57% had documented unmutated IgVH, and 39% had documented 17p deletion. (…)
208573, 05/15/2019	Venetoclax (7)	Oncology	NPM1	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Acute Myeloid Leukemia** Study M14-358

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208573, 05/15/2019	**Venetoclax (8)**	Oncology	FLT3	Clinical Studies	**14 CLINICAL STUDIES** **14.2 Acute Myeloid Leukemia** Study M14-358 VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy. (See Table 24) (…) Study M14-387 (…) Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose [see Dosage and Administration (2.1)]. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial. (See Table 26) (…)
202497, 08/09/2012	**Vincristine**	Oncology	BCR-ABL1 (Philadelphia chromosome)	Indications and Usage, Adverse Reactions, Clinical Studies	**1 INDICATIONS AND USAGE** **1.1 Adult ALL in Second or Greater Relapse** Marqibo® is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified. **6 ADVERSE REACTIONS** **Integrated Summary of Safety in Relapsed and/or Refractory Ph- Adult Acute Lymphoblastic Leukemia** Marqibo, at a dose of 2.25 mg/m2 weekly, was studied in a total of 83 patients in two trials: study 1 and study 2. Adverse reactions were observed in 100% of patients. The most common adverse reactions (>30%) were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%). (…) **14 CLINICAL STUDIES** **14.1 Acute Lymphoblastic Leukemia** Marqibo was studied in an international, open-label, multi-center, single-arm trial (Study 1). Eligible patients were 18 years of age or older with Philadelphia chromosome negative ALL in second or greater relapse or whose disease progressed after two or greater treatment lines of anti-leukemia therapy. Patients had to have achieved a complete remission (CR) to at least one prior anti-leukemia chemotherapy, defined by a leukemia-free interval of equal or more than 90 days. Patients were not eligible for immediate hematopoietic stem cell transplantation (HSCT) at the time of screening and enrollment. (…)
021266, 04/30/2019	**Voriconazole**	Infectious Diseases	CYP2C19	Clinical Pharmacology	**12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** *Metabolism* In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 [see Drug Interactions (7)]. In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_T) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts. (…) **12.5 Pharmacogenomics** CYP2C19, significantly involved in the metabolism of voriconazole, exhibits genetic polymorphism. Approximately 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_T) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts [see Clinical Pharmacology (12.3)].
204447, 10/19/2018	**Vortioxetine**	Psychiatry	CYP2D6	Dosage and Administration, Clinical Pharmacology	**2 DOSAGE AND ADMINISTRATION** **2.6 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors** The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued [see Drug Interactions (7.3)].

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009218, 08/14/2017	Warfarin (1)	Hematology	CYP2C9	Dosage and Administration, Drug Interactions, 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** **12.3 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'-, 6-, 7-, 8-, and 10- hydroxywarfarin. The CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the in vivo anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance [see Clinical Pharmacology (12.5)]. **12.5 Pharmacogenomics** CYP2C9 and VKORC1 Polymorphisms The S-enantiomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S-warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9, and *11 alleles in Caucasians. Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle through inhibition of VKOR, a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (e.g., –1639G>A) have been associated with variable warfarin dose requirements. VKORC1 and CYP2C9 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose of warfarin [see Dosage and Administration (2.3)].
009218, 08/14/2017	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-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

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‡ Referenced figures and tables may be found in the labeling available at Drugs@FDA.
Blue text represents the most recent addtions and/or changes since last posted version.

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

NDA/ANDA/BLA Number, Label Version Date	Drug	Therapeutic Area*	Biomarker†	Labeling Sections	Labeling Text‡
					Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9, and *11 alleles in Caucasians. Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle through inhibition of VKOR, a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (e.g., –1639G>A) have been associated with variable warfarin dose requirements. VKORC1 and CYP2C9 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose of warfarin [see Dosage and Administration (2.3)].
009218, 08/14/2017	Warfarin (3)	Hematology	PROS1	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.8 Other Clinical Settings with Increased Risks** In the following clinical settings, the risks of COUMADIN therapy may be increased: (…) 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 8 hours and 30 hours, respectively.
009218, 08/14/2017	Warfarin (4)	Hematology	PROC	Warnings and Precautions	**5 WARNINGS AND PRECAUTIONS** **5.8 Other Clinical Settings with Increased Risks** In the following clinical settings, the risks of COUMADIN therapy may be increased: (…) 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 8 hours and 30 hours, respectively.

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