Current FDA-Related Drug Information

Approvals, Submission, and Important Labeling Changes for US Marketed Pharmaceuticals

Danial E. Baker, PharmD, FASHP, FASCP*

This monthly feature will help readers keep current on new drugs, new indications, dosage forms, and safety-related changes in labeling or use. Efforts have been made to ensure the accuracy of this information; however, if there are any questions, please let me know at danial.baker@wsu.edu.

Table 1. New drugs approved by the US Food and Drug Administration: September 25, 2015 through October 18, 2015

Aripiprazole lauroxil – Aristada (Alkermes)	
Comparative agents:	Aripiprazole (<i>Abilify Maintena</i>)
Indication:	Treatment of schizophrenia
Mechanism of action:	Atypical antipsychotic; partial agonist activity D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors
Common adverse effects:	Akathisia
Dosage form & strength:	Injection; 441 mg, 662 mg, and 882 mg single-use pre-filled syringe
Product labeling:	http://aristada.com/hcp/ARISTADA-prescribing-information.pdf
Idarucizumab – Praxbind (Boehringer Ingelheim)	
Comparative agents:	None
Indication:	Reversal of the anticoagulant effects of dabigatran is needed in situations such as emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding
Mechanism of action:	Humanized monoclonal antibody fragment (Fab)
Common adverse effects:	Headache, hypokalemia, delirium, constipation, pyrexia, and pneumonia
Dosage form & strength:	Single-use vial for injection: 2.5 g/50 mL
Product labeling:	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: September 25, 2015 through October 18, 2015

Generic name	Brand name (Company)	Indication and comments
New indications		
Ambrisentan plus tadalafil	<i>Letairis</i> (Gilead Sciences); <i>Cialis</i> (Eli Lilly)	Combination therapy for the treatment of pulmonary arterial hypertension to reduce the risk of worsening disease and to improve exercise ability

(continued)

*Director, Drug Information Center, College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495.

Table 2. New dosage forms and indications approved by the FDA: September 25, 2015 through October 18, 2015 (CONT.)

Ipilimumab plus nivolumab	<i>Yervoy & Opdivo</i> (Bristol-Myers Squibb)	Combination therapy for the treatment of advanced melanoma
Nivolumab	<i>Opdivo</i> (Bristol-Myers Squibb)	Treatment of advanced (metastatic) non-small-cell lung cancer in patients whose disease progressed during or after platinum-based chemotherapy
Pembrolizumab	<i>Keytruda</i> (Merck)	Treatment of patients with metastatic non-small-cell lung cancer (NSCLC) whose tumors express programmed death ligand 1 (PD-L1) as determined by an FDA-approved test, 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 pembrolizumab.

Table 3. Agents pending FDA approval: September 25, 2015 through October 18, 2015

Generic name	Brand name (Company)	Indication and comments
Complete response letter: More information required		
Lifitegrast	(Shire)	Another clinical trial has been requested regarding the use of this drug in the treatment of dry eyes.
Saxagliptin/dapagliflozin	(AstraZeneca)	Fixed-dose combination for the treatment of adult patients with type 2 diabetes
Agents scheduled for review by an FDA advisory panel		
Enclomiphene citrate	(Repros Therapeutics)	Treatment of secondary hypogonadism in fertile men (>15 million sperm/mL; younger than 60 years of age, and body mass index [BMI] > 25 kg/m ²)
Gepirone hydrochloride	(Fabre-Kramer Pharmaceuticals)	Major depression disorder
Lesinurad	(Ardea Biosciences)	Hyperuricemia associated with gout, in combination with xanthine oxidase inhibitor
Reslizumab	(Teva Pharmaceutical)	Reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above), with asthma and elevated blood eosinophils, who are inadequately controlled on inhaled corticosteroids
Sugammadex sodium	(Organon)	Reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Abacavir <i>Ziagen</i> (ViiV HealthCare)	BOXED WARNING WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	<p>Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with 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. Abacavir is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir or reinitiation of therapy with abacavir, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue abacavir immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, NEVER restart abacavir 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. <p>Lactic Acidosis and Severe Hepatomegaly with Steatosis</p> <ul style="list-style-type: none"> Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue abacavir if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> New information regarding the HLA-B*5701 allele <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Hypersensitivity reactions information <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Hypersensitivity reactions information <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299326.htm</p>
Abacavir/lamivudine <i>Epzicom</i> (ViiV HealthCare)	<p>BOXED WARNING - updated</p> <p>WARNING: HYPERSENSITIVITY REACTIONS; LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY; and EXACERBATIONS OF HEPATITIS B</p> <p>Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of abacavir and lamivudine. 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. <i>Epzicom</i> is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with <i>Epzicom</i> or reinitiation of therapy with <i>Epzicom</i>, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue <i>Epzicom</i> immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to <i>Epzicom</i>, NEVER restart <i>Epzicom</i> 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.

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	<p>Lactic Acidosis and Severe Hepatomegaly with Steatosis</p> <ul style="list-style-type: none"> Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue <i>Epzicom</i> if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. <p>Exacerbations of Hepatitis B</p> <ul style="list-style-type: none"> Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is a component of <i>Epzicom</i>. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue <i>Epzicom</i> and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Hypersensitivity reactions information <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Hypersensitivity reactions information <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm465862.htm</p>
Abacavir sulfate, dolutegravir, lamivudine <i>Triumeq</i> (ViiV HealthCare)	<p>BOXED WARNING</p> <p>WARNING: HYPERSENSITIVITY REACTIONS; LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY; and EXACERBATIONS OF HEPATITIS B</p> <p>Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of <i>Triumeq</i> (abacavir, dolutegravir, and lamivudine). 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. <i>Triumeq</i> is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with <i>Triumeq</i> or reinitiation of therapy with <i>Triumeq</i>, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue <i>Triumeq</i> immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to <i>Triumeq</i>, NEVER restart <i>Triumeq</i> 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. <p>Lactic Acidosis and Severe Hepatomegaly with Steatosis</p> <ul style="list-style-type: none"> Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals. Discontinue <i>Triumeq</i> if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name <i>Brand name</i> (Company)	Warning
Abacavir, lamivudine, zidovudine <i>Trizivir</i> (ViiV HealthCare)	<p>Exacerbations of Hepatitis B</p> <ul style="list-style-type: none"> Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, a component of <i>Triumeq</i>. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue <i>Triumeq</i> and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> New information regarding the HLA-B*5701 allele <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Hypersensitivity reactions information <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm461230.htm</p>
	<p>BOXED WARNING</p> <p>WARNING: HYPERSENSITIVITY REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B</p> <p>Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of <i>Trizivir</i> (abacavir, lamivudine, and zidovudine). 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. <i>Trizivir</i> is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with <i>Trizivir</i> or reinitiation of therapy with <i>Trizivir</i>, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue <i>Trizivir</i> immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible. Following a hypersensitivity reaction to <i>Trizivir</i>, NEVER restart <i>Trizivir</i> 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. <p>Hematologic Toxicity</p> <ul style="list-style-type: none"> Zidovudine, a component of <i>Trizivir</i>, has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease. <p>Myopathy</p> <ul style="list-style-type: none"> Prolonged use of zidovudine has been associated with symptomatic myopathy. Lactic acidosis and severe hepatomegaly with steatosis lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue <i>Trizivir</i> if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. <p>Lactic Acidosis and Severe Hepatomegaly with Steatosis</p> <ul style="list-style-type: none"> Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue <i>Trizivir</i> if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	<p>Exacerbations of Hepatitis B</p> <ul style="list-style-type: none"> Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, a component of <i>Trizivir</i>. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue <i>Trizivir</i> and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> New information regarding the HLA-B*5701 allele <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> The following sections were updated: Hypersensitivity Reactions, Lactic Acidosis and Severe Hepatomegaly with Steatosis, Patients with Hepatitis B Virus Co-infection, Use with Interferon- and Ribavirin-based Regimens, Related Products that are Not Recommended <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Hypersensitivity reactions information <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm465864.htm</p>
ACE inhibitors (various)	<p>WARNINGS</p> <p>Hyperkalemia</p> <ul style="list-style-type: none"> Risk factors: Other drugs that raise serum potassium levels. Monitor serum potassium in such patients. <p>DRUG INTERACTIONS</p> <p>Agents Increasing Serum Potassium</p> <ul style="list-style-type: none"> Coadministration of <i>Altace</i> with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm233254.htm</p>
Bevacizumab <i>Avastin</i> (Genentech)	<p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Add: Non-mandibular osteonecrosis and posterior reversible encephalopathy syndrome (PRES) <p>USE IN SPECIFIC POPULATIONS</p> <p>Pediatric Use</p> <ul style="list-style-type: none"> Added: Information on non-mandibular osteonecrosis. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275758.htm</p>
Canagliflozin <i>Invokana</i> (Janssen Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Bone Fracture</p> <ul style="list-style-type: none"> An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin.
Canagliflozin/metformin <i>Invokamet</i> (Janssen Pharmaceuticals)	<p>ADVERSE REACTIONS</p> <p>Clinical Studies Experience</p> <p>Falls</p> <ul style="list-style-type: none"> In a pool of 9 clinical trials with mean duration of exposure to canagliflozin of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The higher risk of falls for patients treated with canagliflozin was observed within the first few weeks of treatment.

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name <i>Brand name</i> (Company)	Warning
	<p>Bone Fracture</p> <ul style="list-style-type: none"> The occurrence of bone fractures was evaluated in a pool of 9 clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (eg, fall from no more than standing height), and affect the upper extremities. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm400577.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm441303.htm</p>
Clozapine (various)	<p>BOXED WARNING WARNING: SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</p> <p>Severe Neutropenia</p> <ul style="list-style-type: none"> Clozapine treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/μL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with clozapine a baseline ANC must be at least 1500/μL for the general population and must be at least 1000/μL for patients with documented benign ethnic neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (eg, fever, weakness, lethargy, or sore throat). Because of the risk of severe neutropenia, clozapine is available only through a restricted program under a risk evaluation mitigation strategy (REMS) called the Clozapine REMS Program. <p>CONTRAINDICATIONS Hypersensitivity</p> <ul style="list-style-type: none"> Clozapine is contraindicated in patients with a history of serious hypersensitivity to clozapine (eg, photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson syndrome) or any other component of clozapine. <p>WARNINGS AND PRECAUTIONS Severe Neutropenia</p> <ul style="list-style-type: none"> Update the neutropenia monitoring algorithms and associated clozapine treatment recommendations and to accommodate for clozapine treatment for patients with benign ethnic neutropenia <p>Clozapine REMS Program</p> <ul style="list-style-type: none"> Updated <p>ADVERSE REACTIONS – Postmarketing Experience Urogenital System</p> <ul style="list-style-type: none"> Added: Retrograde ejaculation. <p>SPECIAL POPULATIONS Hospice Patients</p> <ul style="list-style-type: none"> For hospice patients (ie, terminally ill patients with an estimated life expectancy of 6 months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient’s terminal illness. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm201106.htm</p>

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Crizotinib <i>Xalkori</i> (PF Prism CV)	WARNINGS AND PRECAUTIONS <ul style="list-style-type: none"> • New subsection: Severe visual loss http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295722.htm
Diazoxide <i>Proglycem</i> (Teva)	WARNINGS Pulmonary Hypertension in Neonates and Infants <ul style="list-style-type: none"> • Postmarketing reports of pulmonary hypertension in infants and neonates treated with diazoxide. The cases were reversible upon discontinuation of the drug. Monitor patients, especially those with risk factors for pulmonary hypertension, for respiratory distress and discontinue diazoxide if pulmonary hypertension is suspected. ADVERSE REACTIONS Other frequent adverse reactions <ul style="list-style-type: none"> • Cardiovascular: ... Pulmonary hypertension has been reported in neonates and young infants http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm466194.htm
Doxycycline hyclate <i>Doryx</i> (Mayne Pharma)	WARNINGS AND PRECAUTIONS Intracranial Hypertension <ul style="list-style-type: none"> • Intracranial hypertension (IH; pseudotumor cerebri) has been associated with the use of tetracyclines including <i>Doryx</i>. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss: papilledema can be found on funduscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline-associated IH. Avoid concomitant use of isotretinoin and <i>Doryx</i> because isotretinoin is also known to cause pseudotumor cerebri. Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize. ADVERSE REACTIONS <ul style="list-style-type: none"> • Intracranial hypertension: Intracranial hypertension (IH; pseudotumor cerebri) has been associated with the use of tetracyclines... http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm453969.htm
Exenatide <i>Bydureon</i> (AstraZeneca)	WARNINGS AND PRECAUTIONS Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin <ul style="list-style-type: none"> • The risk of hypoglycemia is increased when exenatide is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm400570.htm
Gabapentin <i>Neurontin</i> (Pfizer)	WARNINGS AND PRECAUTIONS Anaphylaxis and Angioedema <ul style="list-style-type: none"> • <i>Neurontin</i> can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue <i>Neurontin</i> and seek immediate medical care should they experience signs or symptoms of anaphylaxis or angioedema. ADVERSE REACTIONS Postmarketing Experience <ul style="list-style-type: none"> • Added: Changes in libido, ejaculation disorders and anorgasmia http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm249683.htm

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Graisetron <i>Sancuso</i> (ProStrakan)	<p>WARNINGS</p> <p>External Heat Sources</p> <ul style="list-style-type: none"> A heat pad should not be applied over or in vicinity of <i>Sancuso</i> patch. Patients should avoid prolonged exposure to heat as plasma concentration continues increasing during the period of heat exposure. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> General Disorders and Administration Site Conditions: Application site reactions (pain, pruritus, erythema, rash, irritation, vesicles, burn, discoloration, urticaria); patch non-adhesion Cardiac Disorders: Bradycardia, chest pain, palpitations, sick sinus syndrome <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm466191.htm</p>
Lamivudine/zidovudine <i>Combivir</i> (ViiV HealthCare)	<p>BOXED WARNING</p> <p>WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B</p> <p>Hematologic Toxicity</p> <ul style="list-style-type: none"> Zidovudine, a component of <i>Combivir</i> (lamivudine and zidovudine) tablets, has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease. <p>Myopathy</p> <ul style="list-style-type: none"> Prolonged use of zidovudine has been associated with symptomatic myopathy. <p>Lactic Acidosis and Severe Hepatomegaly with Steatosis</p> <ul style="list-style-type: none"> Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue <i>Combivir</i> if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. <p>Exacerbations of Hepatitis B</p> <ul style="list-style-type: none"> Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, which is one component of <i>Combivir</i>. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue <i>Combivir</i> and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Updated sections: Lactic Acidosis and Severe Hepatomegaly with Steatosis, Patients with Hepatitis B Virus Co-infection, Related Products that are Not Recommended, Use with Interferon- and Ribavirin-based Regimens <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Information related to immune reconstitution syndrome and fat redistribution <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm465867.htm</p>
Metreleptin <i>Myalept</i> (Amylin Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <p>Hypersensitivity</p> <ul style="list-style-type: none"> Known hypersensitivity reactions have included anaphylaxis <p>WARNINGS AND PRECAUTIONS</p> <p>Hypersensitivity</p> <ul style="list-style-type: none"> Reports of generalized hypersensitivity (eg, anaphylaxis) <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm466192.htm</p>

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Obinutuzumab <i>Gazyva</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Tumor Lysis Syndrome</p> <ul style="list-style-type: none"> Tumor Lysis Syndrome (TLS), including fatal cases, has been reported. Patients with high tumor burden, high circulating lymphocyte count ($> 25 \times 10^9/L$) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (eg, allopurinol or rasburicase) and hydration prior to the infusion of obinutuzumab. During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm404996.htm</p>
Pazopanib <i>Votrient</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Interstitial Lung Disease (ILD)/Pneumonitis</p> <ul style="list-style-type: none"> ILD/pneumonitis, which can be fatal, has been reported. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue pazopanib in patients developing ILD or pneumonitis. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> ILD/pneumonitis <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm</p>
Pegfilgrastim <i>Neulasta</i> (Amgen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Glomerulonephritis</p> <ul style="list-style-type: none"> Glomerulonephritis has occurred in patients receiving pegfilgrastim. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of pegfilgrastim. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose reduction or interruption of pegfilgrastim. <p>Leukocytosis</p> <ul style="list-style-type: none"> White blood cell (WBC) counts of $100 \times 10^9/L$ or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended. <p>Capillary Leak Syndrome</p> <ul style="list-style-type: none"> Capillary leak syndrome has been reported after G-CSF administration and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity, and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262864.htm</p>
PDE5 inhibitors Avanafil, Sildenafil, Tadalafil, Vardenafil (various)	<p>CONTRAINDICATIONS</p> <p>Guanylate Cyclase (GC) Stimulators</p> <ul style="list-style-type: none"> Do not use <drug name> in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including <drug name> may potentiate the hypotensive effects of GC stimulators. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm466053.htm</p>

(continued)

Table 4. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name <i>Brand name</i> (Company)	Warning
Ticagrelor <i>Brilinta</i> (AstraZeneca)	<p>BOXED WARNING</p> <p>WARNING: (A) BLEEDING RISK, (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS</p> <p>A. BLEEDING RISK</p> <ul style="list-style-type: none"> • Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal bleeding. • Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage. • Do not start ticagrelor in patients undergoing urgent coronary artery bypass graft surgery (CABG). • If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events. <p>B. ASPIRIN DOSE AND TICAGRELOR EFFECTIVENESS</p> <ul style="list-style-type: none"> • Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm338265.htm</p>
Vigabatrin <i>Sabril</i> (Lundbeck)	<p>WARNINGS AND PRECAUTIONS</p> <p>Magnetic Resonance Imaging (MRI) Abnormalities in Infants</p> <ul style="list-style-type: none"> • Neurotoxicity and brain histopathological changes were observed in dogs exposed to vigabatrin during the juvenile period of development. .. <p>Neurotoxicity</p> <ul style="list-style-type: none"> • Administration of vigabatrin to juvenile dogs produced vacuolar changes in the brain gray matter (including the septal nuclei, hippocampus, hypothalamus, thalamus, cerebellum, and globus pallidus). Neurobehavioral effects of vigabatrin were not assessed in the juvenile dog. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm335401.htm</p>

^aPractitioners are encouraged to check the US Food and Drug Administration's MEDWATCH Web site (<http://www.fda.gov/medwatch/safety.htm>) for updated information.