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 (FDA): March 16, 2014 through April 17, 2015

Cholic acid – <i>Cholbam</i> (Asklepiion)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs); adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption
<i>Mechanism of action:</i>	Replacement of missing cholic acid in the endogenous bile acids
<i>Common adverse effects:</i>	Diarrhea, reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy
<i>Dosage form & strength:</i>	Capsules; 50 mg and 250 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205750s000lbl.pdf
Anthrax Immune Globulin Intravenous (Human) – <i>Anthrasil</i> (Emergent BioSolutions)	
<i>Comparative agents:</i>	Raxibacumab
<i>Indication:</i>	Treatment of inhalation anthrax in combination with appropriate antibacterial drugs
<i>Mechanism of action:</i>	Immune globulin; designed to neutralize toxins produced by the anthrax bacteria
<i>Common adverse effects:</i>	Headache, back pain, nausea, and infusion site pain and swelling
<i>Dosage form & strength:</i>	Injection
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM439812.pdf

(continued)

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

Current FDA-Related Drug Information

Table 1. New drugs approved by the US Food and Drug Administration (FDA): March 16, 2014 through April 17, 2015 (CONT.)

Ivabradine – Corlanor (Amgen)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq 35\%$, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use
<i>Mechanism of action:</i>	Hyperpolarization-activated cyclic nucleotide-gated channel blocker
<i>Common adverse effects:</i>	Bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes)
<i>Dosage form & strength:</i>	Tablets; 5 & 7.5 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206143Orig1s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: March 16, 2015 through April 17, 2015

Generic name	Brand name (Company)	Indications and comment
New dosage forms/strength/route of administration		
Albuterol	<i>ProAir</i> Respi Click (Teva)	New device
Deferasirox	<i>Jadenu</i> (Novartis)	New formulation of <i>Exjade</i> that allows the patient to swallow the tablet whole. <i>Exjade</i> was a tablet used to create a suspension before administration.
Ticagrelor	<i>Brilinta</i> (AstraZeneca)	Can be crushed and administered in water by swallowing or via nasogastric tube
Vilazodone	<i>Viibryd</i> (Forest)	New clinical data in the treatment of major depressive disorder in adults that supports a dose of 20 mg/day as the minimum effective dose
New indications		
Aflibercept	<i>Eylea</i> (Regeneron Pharmaceuticals)	Treatment of diabetic retinopathy in patients with diabetic macular edema
Asenapine	<i>Saphris</i> (Actavis)	Treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients (ages 10 to 17 years)
Ivacaftor	<i>Kalydeco</i> (Vertex Pharmaceuticals)	Children aged 2 to 5 years with cystic fibrosis who have one of 10 mutations in the cystic fibrosis transmembrane conductance regulator gene

Table 3. Agents pending FDA approval: March 16, 2015 through April 17, 2015

Generic name	Brand name (Company)	Indication and comments
Recommended for approval by an FDA advisory panel		
Fluticasone furoate/vilanterol	<i>Breo Ellipta</i> (GlaxoSmithKline)	Advisory panel voted 16-4 for approved for once daily treatment of asthma in adults 18 years and older. Advisory panel voted 19-1 against approval for use of the drug in the treatment of asthma in children 12 to 17 years.

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

Generic name Brand name (Company)	Warning
Alprostadil <i>Edex</i> for injection (Auxilium Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • In men who have conditions that predispose them to priapism, such as sickle cell anemia or sickle cell trait, multiple myeloma, or leukemia [see Warnings and Precautions (5.1)]. • For the treatment of erectile dysfunction in men with fibrotic conditions of the penis, such as cavernosal fibrosis or Peyronie’s disease [see Warnings and Precautions (5.2)] • In men with penile implants <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm441961.htm</p>
Amiodarone <i>Cordarone</i> (Pfizer/Wyeth)	<p>WARNINGS</p> <p>Worsened Arrhythmia</p> <ul style="list-style-type: none"> • [added]...The risk of exacerbation may be increased when other risk factors are present such as electrolytic disorders or use of concomitant antiarrhythmics or other interacting drugs (See “Drug Interactions, Other reported interactions with amiodarone”). • [added]...Correct hypokalemia, hypomagnesemia or hypocalcemia whenever possible before initiating treatment with <i>Cordarone</i>, as these disorders can exaggerate the degree of QTc prolongation and increase the potential for TdP. Give special attention to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics and laxatives, systemic corticosteroids, amphotericin B (IV) or other drugs affecting electrolyte levels. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm239971.htm</p>
Capecitabine <i>Xeloda</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Dihydropyrimidine Dehydrogenase Deficiency</p> <ul style="list-style-type: none"> • 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 <i>Xeloda</i> (eg, 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 <i>Xeloda</i>. • Withhold or permanently discontinue <i>Xeloda</i> 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 <i>Xeloda</i> 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. <p>ADVERSE REACTIONS</p> <p>Clinically Relevant Adverse Events in <5% of Patients</p> <ul style="list-style-type: none"> • Monotherapy (metastatic colorectal cancer, adjuvant colorectal cancer, metastatic breast cancer) • Postmarketing: Toxic leukoencephalopathy <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm422806.htm</p>

(continued)

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

Cetuximab <i>Erbitux</i> (Bristol-Myers Squibb)	<p>WARNINGS AND PRECAUTIONS</p> <p>Dermatologic Toxicity</p> <ul style="list-style-type: none"> Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with <i>Erbitux</i>. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis). <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, life-threatening and fatal bullous mucocutaneous disease <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289979.htm</p>
Diltiazem <i>Cardizem LA</i> (AbbVie)	<p>WARNINGS AND PRECAUTIONS</p> <p>Bradycardia or AV Block [section added]</p> <ul style="list-style-type: none"> <i>Cardizem LA</i> may cause abnormally slow heart rates or second- or third-degree AV block. Patients with sick sinus syndrome are at increased risk of bradycardia. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem. Monitor for effects on heart rate and cardiac conduction. <p>Acute Hepatic Injury [section edited]</p> <ul style="list-style-type: none"> Significant elevations in liver enzymes such as alkaline phosphatase, LDH, AST (SGOT), ALT (SGPT), and signs of acute hepatic injury have been reported with diltiazem therapy. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have also been observed. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. <p>Severe Skin Reactions [section added]</p> <ul style="list-style-type: none"> Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and/or exfoliative dermatitis have been reported. <p>DRUG INTERACTIONS</p> <p>Agents Known to Impair Cardiac Contractility and Conduction [section added]</p> <ul style="list-style-type: none"> Using other agents known to affect cardiac conduction or contractility with diltiazem may increase the risk of bradycardia, AV block, and heart failure. <p>Interactions with Cytochrome P-450 3A4 Substrates, Inhibitors and Inducers [section added]</p> <ul style="list-style-type: none"> Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Simvastatin: Limit daily dose of simvastatin 10 mg and diltiazem to 240 mg, if co-administration of both drugs are required. Rifampin: Avoid co-administration of rifampin with diltiazem. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm442222.htm</p>
Ferumoxytol <i>Feraheme</i> (AMAG Pharmaceuticals)	<p>Boxed Warning added and Warning Section changed: Potentially fatal allergic reactions</p> <p>Contraindication: Avoid this product in patients who have had an allergic reaction to any intravenous (IV) iron replacement product.</p> <p>http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery</p>

(continued)

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

HIV protease inhibitor drugs: Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir (Various manufacturers)	<p>Class warning:</p> <p>Risk of Serious Adverse Reactions Due to Drug Interactions</p> <ul style="list-style-type: none"> Initiation of <product>, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving < product >, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of <product >, respectively. <p>These interactions may lead to:</p> <ul style="list-style-type: none"> Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications. Clinically significant adverse reactions from greater exposures of <product>. Loss of therapeutic effect of <product> and possible development of resistance. <p>See Table in the insert for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during <product> therapy; review concomitant medications during <product> therapy; and monitor for the adverse reactions associated with the concomitant medications.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm442379.htm</p>
Levetiracetam <i>Keppra</i> (UCB)	<p>WARNINGS AND PRECAUTIONS</p> <p>Behavioral Abnormalities and Psychotic Symptoms</p> <ul style="list-style-type: none"> <i>Keppra</i> may cause behavioral abnormalities and psychotic symptoms. Patients treated with <i>Keppra</i> should be monitored for psychiatric signs and symptoms. <p>Somnolence and Fatigue</p> <ul style="list-style-type: none"> <i>Keppra</i> may cause somnolence and fatigue. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on <i>Keppra</i> to gauge whether it adversely affects their ability to drive or operate machinery. Asthenia Somnolence and asthenia occurred most frequently within the first 4 weeks of treatment. In general, the incidences of somnolence and fatigue in the pediatric partial onset seizure studies and in pediatric and adult myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult partial onset seizure studies. <p>Hematologic Abnormalities</p> <ul style="list-style-type: none"> <i>Keppra</i> can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in red blood cell (RBC) counts, hemoglobin, and hematocrit, and increases in eosinophil counts. Decreased white blood cell (WBC) and neutrophil counts also occurred in clinical trials. Cases of agranulocytosis have been reported in the postmarketing setting. <p>Increase in Blood Pressure</p> <ul style="list-style-type: none"> Monitor patients 1 month to <4 years of age for increases in diastolic blood pressure. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm284241.htm</p>

(continued)

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

Panitumumab <i>Vectibix</i> (Amgen)	<p>WARNING AND PRECAUTIONS</p> <p>Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with RAS-Mutant mCRC</p> <ul style="list-style-type: none"> <i>Vectibix</i> 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”. 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. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319207.htm</p>
Sofosbuvir <i>Sovaldi & Harvoni</i> (Gilead)	<p>Avoid use in patients requiring treatment of amiodarone. Combination of hepatitis C treatment that contain sofosbuvir plus another direct acting antiviral drug with amiodarone have resulted in serious or life-threatening symptomatic bradycardia.</p> <p>http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery</p>
Ulipristal acetate <i>Ella</i> (Afaxys)	<p>WARNINGS AND PRECAUTIONS</p> <p>Fertility Following Use</p> <ul style="list-style-type: none"> [added]...After use of <i>Ella</i>, a reliable barrier method of contraception should be used with subsequent acts of intercourse that occur in that same menstrual cycle. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm306971.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.