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): April 19, 2015 through May 15, 2015

Coagulation factor IX [recombinant] – <i>Ixinity</i> (Emergent BioSolutions)	
<i>Comparative agents:</i>	Factor IX complex
<i>Indication:</i>	Hemophilia B
<i>Mechanism of action:</i>	Coagulation factor replacement
<i>Common adverse effects:</i>	Headache
<i>Dosage form & strength:</i>	Lyophilized powder; intravenous use after reconstitution – glass vial; 500, 1000, and 1500 international units per vial
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM445106.pdf
Deoxycholic acid – <i>Kybella</i> (Kythera Biopharmaceuticals)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults; moderate-to-severe fat below the chin
<i>Mechanism of action:</i>	Destruction of cell membrane resulting in cell lysis
<i>Common adverse effects:</i>	Nerve injury in the jaw, swelling, bruising, pain, numbness, redness, and areas of hardness in the treatment site
<i>Dosage form & strength:</i>	Injection; 10 mg/mL in 2 mL vials
<i>Product labeling:</i>	https://mykybella.com/wp-content/uploads/2015/04/KYBELLA-Combined-FINAL-Labeling.pdf
Fentanyl iontophoretic transdermal system – <i>IONSYS</i> (The Medicines Co.)	
<i>Comparative agents:</i>	Fentanyl
<i>Indication:</i>	Short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital
<i>Mechanism of action:</i>	Opioid agonist
<i>Common adverse effects:</i>	Headache, hypotension, nausea, vomiting, anemia, dizziness, application site reaction-erythema, pruritus, urinary retention
<i>Dosage form & strength:</i>	Iontophoretic transdermal system; 80 doses of 40 mcg each
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021338s005lbl.pdf

(continued)

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

Table 1. New drugs approved by the US Food and Drug Administration (FDA): April 19, 2015 through May 15, 2015 (CONT.)

Fibrin sealant [human] – Raplixa (ProFibrix BV)	
<i>Comparative agents:</i>	Fibrin
<i>Indication:</i>	Adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical
<i>Mechanism of action:</i>	Fibrin sealant
<i>Common adverse effects:</i>	Procedural pain, nausea, constipation, pyrexia, and hypotension
<i>Dosage form & strength:</i>	Dry, ready-to-use powder
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM445346.pdf

Table 2. New dosage forms and indications approved by the FDA: April 19, 2015 through May 15, 2015

Generic name	Brand name (Company)	Indication and comments
New indications		
Fluticasone furoate and vilanterol inhalation powder	<i>Breo Ellipta</i> (GlaxoSmithKline)	Treatment of asthma in patients 18 years and older
Moxifloxacin	<i>Avelox</i> (Bayer Healthcare)	Treatment of patients with plague
Ramucirumab	<i>Cyramza</i> (Eli Lilly)	Use in combination with FOLFIRI (leucovorin calcium, 5-fluorouracil, and irinotecan) for the treatment of patients with metastatic colorectal cancer whose disease has progressed on a first-line bevacizumab-, oxaliplatin-, and fluoropyrimidine-containing regimen.

Table 3. Agents pending FDA approval: April 19, 2015 through May 15, 2015

Generic name	Brand name (Company)	Indication and comments
Complete response letter: More information required		
Sugammadex	<i>Bridion</i> (Merck)	Drug indicated for the reversal of the effects of muscle relaxants used during surgery; requested more information regarding the allergic reactions associated with the drug.
Recommended for approval by an FDA advisory panel		
Ivacaftor/lumacaftor	<i>Orkambi</i> (Vertex Pharmaceuticals)	Advisory committee recommended approval (12 to 1) for use in people with cystic fibrosis (CF) of ages 12 and older who have two copies of the F508del mutation in the <i>CFTR</i> gene.

Current FDA-Related Drug Information

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

Generic Name Brand Name (Company)	Warning
Acidinium <i>Tudorza Pressair</i> (AstraZeneca)	<p>WARNINGS AND PRECAUTIONS</p> <p>Immediate Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Immediate hypersensitivity reactions, including anaphylaxis, angioedema (including swelling of the lips, tongue, or throat), urticaria, rash, bronchospasm, or itching, have occurred. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446322.htm</p>
Alendronate, etidronate, ibandronate, risedronate, (Various)	<p>Class warning: Updated information regarding the risk of osteonecrosis of the jaw (ONJ) with concomitant use of bisphosphonates and angiogenesis inhibitors.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446286.htm</p>
Amlodipine/ benazepril <i>Lotrel</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (eg, temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema. <p>DRUG INTERACTIONS</p> <p>Benazepril</p> <ul style="list-style-type: none"> Mammalian target of rapamycin (mTOR) inhibitors: The risk of angioedema may be increased in patients receiving coadministration of ACE inhibitors and mTOR inhibitors (eg, temsirolimus, sirolimus, and everolimus). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208617.htm</p>
Azilsartan/ chlorthalidone <i>Edarbyclor</i> (Arbor Pharms)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypokalemia - Serum Electrolyte Imbalances</p> <ul style="list-style-type: none"> Thiazide diuretics can cause hyponatremia and hypokalemia. Drugs that inhibit the renin angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm396553.htm</p>
Canagliflozin, dapagliflozin, and empagliflozin (Various)	<p>Risk of ketoacidosis is being investigated.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm446994.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery</p>
Cetuximab <i>Erbix</i> (Imclone)	<p>WARNINGS 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>Erbix</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 K-Ras or N-Ras and hereafter is referred to as “Ras.” Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials including Study 4 were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment-related toxicity. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289979.htm</p>
Denosumab <i>Prolia</i> (Amgen)	<p>Risk of osteonecrosis of the jaw (ONJ) with the concomitant use of bisphosphonates and angiogenesis inhibitors</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446286.htm</p>

(continued)

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

Diclofenac/ misoprostol <i>Arthrotec</i> (Searle)	<p>WARNINGS</p> <p>Hepatic Effects</p> <ul style="list-style-type: none"> • In another clinical trial where over 17,000 patients received diclofenac for a mean of 18 months, hepatitis was rarely observed. • In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and usually occur within 1-6 months, but can occur at any time during treatment with diclofenac. <p>ADVERSE REACTIONS</p> <p>Metabolic and Nutritional</p> <ul style="list-style-type: none"> • Alanine aminotransferase and aspartate aminotransferase increased <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm239819.htm</p>
Isosorbide dinitrate/ hydralazine <i>BiDil</i> (Arbor Pharms)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Patients who are allergic to organic nitrates. • Do not use in patients who are taking PDE-5 inhibitors, such as avanafil, sildenafil, tadalafil, or vardenafil. Concomitant use can cause severe hypotension, syncope, or myocardial ischemia. • Do not use in patients who are taking the soluble guanylate cyclase (sGC) stimulator riociguat. Concomitant use can cause hypotension. <p>DRUG INTERACTIONS</p> <p>Phosphodiesterase Inhibitors</p> <ul style="list-style-type: none"> • Contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). PDE5 inhibitors such as avanafil, sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates. Do not use in patients who are taking the soluble guanylate cyclase (sGC) stimulator riociguat. Concomitant use can cause hypotension. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446146.htm</p>
Itraconazole <i>Sporanox</i> (Janssen Pharma)	<p>BOXED WARNING</p> <p>Congestive Heart Failure, Cardiac Effects and Drug Interactions</p> <ul style="list-style-type: none"> • Addition of coadministration of the following drugs are contraindicated: ticagrelor, colchicine, fesoterodine, telithromycin and solifenacin. <p>CONTRAINDICATIONS</p> <p>Drug Interactions</p> <ul style="list-style-type: none"> • Coadministration of a number of CYP3A4 substrates are contraindicated. • Plasma concentrations increase for the following drugs: ticagrelor, and, in subjects with varying degrees of renal or hepatic impairment, colchicine, fesoterodine, telithromycin, and solifenacin. <p>PRECAUTIONS</p> <p>Cystic Fibrosis</p> <ul style="list-style-type: none"> • If a cystic fibrosis patient does not respond, consideration should be given to switching to alternative therapy. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm223891.htm</p>
Maraviroc <i>Selzentry</i> (ViiV)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hepatotoxicity</p> <ul style="list-style-type: none"> • Caution should be used when administering to patients with pre-existing liver dysfunction or who are co-infected with hepatitis B and/or C virus. The safety and efficacy of have not maraviroc been specifically studied in patients with significant underlying liver disorders. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm215506.htm</p>
Pazopanib <i>Votrient</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hepatic Toxicity and Hepatic Impairment</p> <ul style="list-style-type: none"> • Patients older than 65 years are at greater risk for hepatotoxicity. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> • Eye Disorders: Retinal detachment/tear. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm</p>

(continued)

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

Pomalidomide <i>Pomalyst</i> (Celgene)	<p>BOXED WARNING</p> <p>VENOUS AND ARTERIAL THROMBOEMBOLISM</p> <ul style="list-style-type: none"> • Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma. Antithrombotic prophylaxis is recommended <p>WARNINGS AND PRECAUTIONS – Updated information added to the following sections: Venous and Arterial Thromboembolism, Hematologic Toxicity, Hepatotoxicity, Hypersensitivity Reactions, Dizziness and Confusional State, Neuropathy, Tumor Lysis Syndrome.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446484.htm</p>
Primaquine (Various)	<p>PRECAUTIONS</p> <ul style="list-style-type: none"> • Due to potential for QT interval prolongation, monitor ECG when using primaquine in patients with cardiac disease, long QT syndrome, a history of ventricular arrhythmias, uncorrected hypokalemia and/or hypomagnesemia, or bradycardia (<50 bpm), and during concomitant administration with QT interval prolonging agents. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> • Cardiac: Cardiac arrhythmia and QT interval prolongation <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446137.htm</p>
Sildenafil <i>Revatio</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319416.htm</p>
Simeprevir <i>Olysio</i> (Janssen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone</p> <ul style="list-style-type: none"> • Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is co-administered with sofosbuvir in combination with another HCV direct acting antiviral. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with co-administration of amiodarone. <p>Hepatic Decompensation and Hepatic Failure</p> <ul style="list-style-type: none"> • Hepatic decompensation and hepatic failure, including fatal cases, have been reported postmarketing in patients treated with <i>Olysio</i> in combination with peginterferon alfa and ribavirin or in combination with sofosbuvir. Most cases were reported in patients with advanced and/or decompensated cirrhosis who are at increased risk for hepatic decompensation or hepatic failure. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between treatment with <i>Olysio</i> and these events has not been established <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm417602.htm</p>
Sunitinib <i>Sutent</i> (CPPI CV)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> • “Left Ventricular Dysfunction” changed to “Cardiovascular Events.” • “Myocardial disorders” changed to “myocardial ischemia, myocardial infarctions.” • Use <i>Sutent</i> with caution in patients who are at risk for, or who have a history of these events.” • Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of <i>Sutent</i> as monotherapy and in combination with bevacizumab. Discontinue <i>Sutent</i> in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm224050.htm</p>

(continued)

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

Tadalafil <i>Adcirca</i> (Lilly)	CONTRAINDICATIONS Concomitant Guanylate Cyclase (GC) Stimulators <ul style="list-style-type: none">Do not use in patients who are using a GC stimulator; riociguat may potentiate the hypotensive effects of GC stimulators. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm396467.htm
Trastuzumab <i>Herceptin</i> (Genentech)	WARNINGS AND PRECAUTIONS Embryo-Fetal Toxicity <ul style="list-style-type: none">If the patient becomes pregnant while taking <i>Herceptin</i> or within 7 months following the last dose of <i>Herceptin</i>, apprise the patient of the potential hazard to a fetus.Advise females of reproductive potential to avoid becoming pregnant while taking <i>Herceptin</i>. If contraceptive methods are being considered, use effective contraception during treatment and for at least 7 months after receiving the last dose of <i>Herceptin</i>. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392225.htm

^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.