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 dosage forms and indications approved by the US Food and Drug Administration (FDA): August 27, 2013 through September 20, 2013

New indications		
Onabotulinumtoxin A	<i>Botox Cosmetic</i> (Allergan)	The temporary improvement in the appearance of moderate to severe lateral canthal lines, known as crow's feet, in adults
Paclitaxel protein-bound particles (albumin bound)	<i>Abraxane</i> for injectable suspension (Abraxis BioScience)	Use for first-line treatment, in combination with gemcitabine, of patients with metastatic adenocarcinoma of the pancreas

Table 2. Agents pending FDA approval: August 27, 2013 through September 20, 2013

Generic name	Brand name (Company)	Indication and comments
Delayed decision by the FDA		
Collagenase clostridium histolyticum	<i>Xiaflex</i> (Auxilium Pharmaceuticals)	Application for use in the treatment of Peyronie's disease delayed until December 6, 2013
Recommended for approval by an FDA advisory panel		
Umeclidinium/vilanterol	(Theravance/GlaxoSmithKline)	Long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema

(continued)

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

Table 2. Agents pending FDA approval: August 27, 2013 through September 20, 2013 (CONT.)

Generic name	Brand name (Company)	Indication and comments
Agents scheduled for review by an FDA advisory panel		
Icosapent ethyl	<i>Vascepa</i> (Amarin Pharmaceuticals)	Supplemental application for the concomitant use with a HMG-CoA reductase inhibitor to reduce triglyceride, non-high-density lipoprotein cholesterol, apolipoprotein B, low-density lipoprotein cholesterol, total cholesterol, and very-low-density cholesterol in adults with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent
Miltefosine	(Paladin Therapeutics)	Treatment of patients with visceral, mucosal, and cutaneous leishmaniasis
Simeprevir	(Janssen Pharmaceuticals)	Treatment of chronic hepatitis C genotype 1, in combination with peginterferon alfa and ribavirin in adults with compensated liver disease
Sweet vernal grass, perennial ryegrass, timothy grass, orchard grass, and Kentucky bluegrass mixed pollens allergen extract	<i>Oralair</i> (Stallergenes)	Sublingual tablet

Table 3. New drug/biologics license applications filed by manufacturer: August 27, 2013 through September 20, 2013

Generic name Brand name (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Idelalisib (Gilead Sciences)	None	Treatment of indolent non-Hodgkin's lymphoma	Phosphoinositide 3-kinase (PI3K) delta inhibitor	Diarrhea, transaminase elevations, neutropenia	Oral	
Siltuximab (Janssen-Cilag International NV)	None	Treatment of patients with multicentric Castleman disease who are HIV-negative and human herpes virus-8 (HHV-8)-negative	Interleukin-6 chimeric monoclonal antibody	Neutropenia, anemia, thrombocytopenia, fatigue, diarrhea, peripheral edema, nausea	Injection	Orphan drug

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

Generic name Brand name (Company)	Warning
Ambrisentan <i>Letairis</i> (Gilead)	<p>CONTRAINDICATIONS</p> <p>Pregnancy</p> <ul style="list-style-type: none"> <i>Letairis</i> was consistently shown to have teratogenic effects when administered to animals. <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Embryo-fetal Toxicity: <i>Letairis</i> may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. . . <i>Letairis</i> REMS Program: <i>Letairis</i> REMS, because of the risk of embryo-fetal toxicity <p>Decreased Sperm Count</p> <ul style="list-style-type: none"> Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan. <i>Letairis</i> may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility. <p>ADVERSE REACTIONS</p> <p>USE IN SPECIFIC POPULATIONS</p> <p>Pregnancy</p> <ul style="list-style-type: none"> Risk Summary: <i>Letairis</i> may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Animal Data: <i>Letairis</i> was teratogenic at oral doses of ≥ 15 mg/kg/day (AUC 51.7 h•μg/mL) in rats and ≥ 7 mg/kg/day (24.7 h•μg/mL) in rabbits. <p>Nursing Mothers</p> <ul style="list-style-type: none"> It is not known whether ambrisentan is present in human milk. <p>Females and Males of Reproductive Potential</p> <ul style="list-style-type: none"> Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and 1 month after stopping treatment with <i>Letairis</i>. Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with <i>Letairis</i> and for 1 month after stopping treatment with <i>Letairis</i>. Infertility – Males: In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV pulmonary artery hypertension (PAH) and normal baseline sperm count were evaluated for effects on testicular function. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm113761.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
Atomoxetine hydrochloride <i>Strattera</i> (Lilly)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Severe Cardiovascular Disorders: <i>Strattera</i> should not be used in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important (eg, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate). <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Effects on Blood Pressure and Heart Rate: <i>Strattera</i> should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate such as certain patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. Aggressive Behavior or Hostility: Patients beginning treatment for attention deficit hyperactivity disorder (ADHD) should be monitored for the appearance or worsening of aggressive behavior or hostility. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm223889.htm</p>
Denosumab <i>Xgeva</i> (Amgen)	<p>CONTRAINDICATIONS</p> <p>Hypocalcemia</p> <ul style="list-style-type: none"> Preexisting hypocalcemia must be corrected prior to initiating therapy with <i>Xgeva</i>. <p>Hypersensitivity</p> <ul style="list-style-type: none"> <i>Xgeva</i> is contraindicated in patients with known clinically significant hypersensitivity to <i>Xgeva</i>. <p>WARNINGS AND PRECAUTIONS</p> <p>Drug Product with Same Active Ingredient</p> <ul style="list-style-type: none"> <i>Xgeva</i> includes the same active ingredient (denosumab) found in <i>Prolia</i>. Patients receiving <i>Xgeva</i> should not take <i>Prolia</i>. <p>Hypersensitivity</p> <ul style="list-style-type: none"> Clinically significant hypersensitivity including anaphylaxis has been reported with use of <i>Xgeva</i>. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritis, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue <i>Xgeva</i> therapy permanently. <p>Atypical Subtrochanteric and Diaphyseal Femoral Fracture</p> <ul style="list-style-type: none"> Atypical femoral fracture has been reported with <i>Xgeva</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm343116.htm</p>

(continued)

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

Generic name Brand name (Company)	Warning
Doxorubicin HCl <i>Doxil</i> (Janssen)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Secondary Oral Neoplasm: Secondary oral cancers, primarily squamous cell carcinoma, have been reported from postmarketing experience in patients with long-term (more than 1 year) exposure to <i>Doxil</i>. <p>ADVERSE REACTIONS Postmarketing Experience</p> <ul style="list-style-type: none"> Secondary oral neoplasms <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368248.htm</p>
Gadodiamide <i>Omniscan</i> injection (GE Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Prior hypersensitivity reaction to <i>Omniscan</i> <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Hypersensitivity Reaction: Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory, and/or cutaneous manifestations, resulting in death have occurred. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368234.htm</p>
Gadofosveset trisodium <i>Ablavar</i> (Lantheus Medical Imaging)	<p>WARNINGS AND PRECAUTIONS Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Have trained personnel and emergency resuscitative equipment available prior to and during <i>Ablavar</i> administration. If such a reaction occurs, stop <i>Ablavar</i> and immediately begin appropriate therapy. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm238185.htm</p>
Gadoversetamide <i>Optimark</i> injection (Mallinckrodt)	<p>CONTRAINDICATIONS Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Severe hypersensitivity reactions including anaphylaxis have been observed with administration of gadolinium products including <i>Optimark</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368229.htm</p>
Ibritumomab tiuxetan <i>Zevalin</i> (Spectrum Pharms)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Serious Infusion Reactions: Rituximab, alone or as a component of the <i>Zevalin</i> therapeutic regimen, can cause severe, including fatal, infusion reactions. Prolonged and Severe Cytopenias: Cytopenias with delayed onset and prolonged duration, some complicated by hemorrhage and severe infection, are the most common severe adverse reactions of the <i>Zevalin</i> therapeutic regimen. . . Risk of Developing Myelodysplastic Syndrome, Leukemia, and Other Malignancies: The radiation dose resulting from therapeutic exposure to Y-90 radiolabeled <i>Zevalin</i> may result in secondary malignancies. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368309.htm</p>

(continued)

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

Generic name Brand name (Company)	Warning
Levonorgestrel-releasing intrauterine system <i>Mirena</i> (Bayer Healthcare)	WARNINGS AND PRECAUTIONS Perforation <ul style="list-style-type: none"> Clinical trials with <i>Mirena</i> excluded breast-feeding women. An interim analysis from a large postmarketing safety study shows an increased risk of perforation in lactating women. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367344.htm
Levonorgestrel-releasing intrauterine system <i>Skyla</i> (Bayer Healthcare)	WARNINGS AND PRECAUTIONS Perforation <ul style="list-style-type: none"> Clinical trials with <i>Skyla</i> excluded breast-feeding women. An interim analysis from a large postmarketing safety study with other IUDs shows an increased risk of perforation in lactating women. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367349.htm
Mesalamine <i>Lialda</i> delayed-release tablets (Shire)	WARNINGS AND PRECAUTIONS <ul style="list-style-type: none"> Interference with Laboratory Tests: Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection because of the similarity in the chromatograms of normetanephrine and mesalamine’s main metabolite, N-acetylaminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367419.htm
Methamphetamine hydrochloride <i>Desoxyn</i> (Ovation Pharmaceuticals)	WARNINGS Peripheral Vasculopathy, Including Raynaud’s Phenomenon <ul style="list-style-type: none"> Stimulants, including <i>Desoxyn</i>, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud’s phenomenon. PRECAUTIONS Information for Patients <ul style="list-style-type: none"> Circulation Problems in Fingers and Toes (Peripheral Vasculopathy, Including Raynaud’s Phenomenon): Instruct patients beginning treatment with <i>Desoxyn</i> about the risk of peripheral vasculopathy, including Raynaud’s phenomenon. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368200.htm
Methylnaltrexone bromide <i>Relistor</i> (Salix Pharms)	WARNINGS AND PRECAUTIONS Gastrointestinal Perforation <ul style="list-style-type: none"> Cases of gastrointestinal (GI) perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (ie, cancer, peptic ulcer, Ogilvie’s syndrome). http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm221639.htm
Methylphenidate <i>Quillivant XR</i> (Nextwave Pharms)	WARNINGS AND PRECAUTIONS <ul style="list-style-type: none"> Peripheral Vasculopathy, Including Raynaud’s Phenomenon: Stimulants, including <i>Quillivant XR</i>, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud’s phenomenon. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367479.htm

(continued)

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

Generic name Brand name (Company)	Warning
Opioid analgesics; extended-release and long-acting formulations	<p>Class-Labeling Changes</p> <p>Updated indication: Extended-release and long-acting (ER/LA) opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>New boxed warning: Caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management according to protocols developed by neonatology experts. Symptoms may include poor feeding, rapid breathing, trembling, and excessive or high-pitched crying.</p> <p>Various changes in the Dosage and Administration; Warnings and Precautions; Drug Interactions; Use in Specific Populations; Patient Counseling Information; and Medication Guide sections of the labeling.</p> <p>http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm</p>
Pazopanib <i>Votrient</i> (GlaxoSmithKline)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Thrombotic Microangiopathy: Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), has been reported in clinical trials of <i>Votrient</i> as monotherapy, in combination with bevacizumab, and in combination with topotecan. <p>ADVERSE REACTIONS</p> <p>Clinical Trials Experience</p> <p>Potential serious adverse reactions with <i>Votrient</i> include:</p> <ul style="list-style-type: none"> Thrombotic microangiopathy Bradycardia: In the randomized trial of <i>Votrient</i> for the treatment of renal cell carcinoma, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with <i>Votrient</i> and in 11% (16/144) of patients in the placebo arm. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm</p>
Polyethylene glycol-3350 and electrolytes <i>Colyte</i> (Meda Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Serious Fluid and Serum Chemistry Abnormalities</p> <ul style="list-style-type: none"> Advise patients to hydrate adequately before, during, and after the use of <i>Colyte</i>. <p>ADVERSE REACTIONS</p> <p>Colonic Mucosal Ulcerations and Ischemic Colitis</p> <ul style="list-style-type: none"> Administration of osmotic laxative products may produce colonic mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367649.htm</p>

(continued)

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

Generic name Brand name (Company)	Warning
Rivaroxaban <i>Xarelto</i> (Janssen)	<p>BOXED WARNING</p> <ul style="list-style-type: none"> Premature discontinuation of <i>Xarelto</i> increases the risk of thrombotic events, and spinal/epidural hematoma. <p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including <i>Xarelto</i>, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. Patients with Prosthetic Heart Valves: The safety and efficacy of <i>Xarelto</i> have not been studied in patients with prosthetic heart valves. Therefore, use of <i>Xarelto</i> is not recommended in these patients. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367392.htm</p>
Roflumilast <i>Daliresp</i> (Forest)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Cases of suicidal ideation and behavior, including completed suicide, have been observed in the postmarketing setting in patients with or without a history of depression. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368228.htm</p>
Rosuvastatin calcium <i>Crestor</i> (AstraZeneca)	<p>WARNINGS AND PRECAUTIONS</p> <p>Endocrine Effects</p> <ul style="list-style-type: none"> Based on clinical trial data with <i>Crestor</i>, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus. <p>ADVERSE REACTIONS</p> <p>Clinical Studies Experience</p> <p>Table 3 - Adverse Reactions Reported in $\geq 2\%$ of Patients Treated with Crestor and $>$ Placebo in the Jupiter Trial</p> <ul style="list-style-type: none"> Diabetes mellitus <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Thrombocytopenia <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm200635.htm</p>
Sunitinib malate <i>Sutent</i> (CPPI CV)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Thyroid Dysfunction: Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of <i>Sutent</i> treatment. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Hepatobiliary disorders: cholecystitis, particularly acalculous cholecystitis <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm224050.htm</p>

^aPractitioners are encouraged to check the FDA’s MEDWATCH Web site (<http://www.fda.gov/medwatch/safety.htm>) for updated information.