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): January 18, 2014 through February 16, 2014

Elosulfase alfa– <i>Vimizim</i> (BioMarin Pharmaceuticals)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of mucopolysaccharidosis type IVA (Morquio A syndrome)
<i>Mechanism of action:</i>	N-acetylgalactosamine-6-sulfate sulfatase enzyme
<i>Common adverse effects:</i>	Fever, vomiting, headache, nausea, abdominal pain, chills, and fatigue
<i>Dosage form & strength:</i>	Injection
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125460s000lbl/pdf
Tasimelteon – <i>Hetlioz</i> (Vanda Pharmaceuticals)	
<i>Comparative agents:</i>	Melatonin
<i>Indication:</i>	Treatment of non-24-hour sleep-wake disorder
<i>Mechanism of action:</i>	Melatonin receptor agonist
<i>Common adverse effects:</i>	Headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection
<i>Dosage form & strength:</i>	Capsules: 20 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205677s000lbl.pdf

*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: January 18, 2014 through February 16, 2014

Generic name	Brand name (Company)	Indication and comments
New dosage forms/ strength/route of administration		
Glatiramer acetate	<i>Copaxone</i> (Teva)	40 mg subcutaneous injection (40 mg/mL) 3 times a week for the treatment of relapsing forms of multiple sclerosis.
New indications		
Ibrutinib	<i>Imbruvica</i> (Pharmacyclics)	Accelerated approval for treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. Previously approved for treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

Table 3. Agents pending FDA approval: January 18, 2014 through February 16, 2014

Generic name	Brand name (Company)	Indication and comments
Complete response letter: approvable		
Rivaroxaban	<i>Xarelto</i> (Johnson & Johnson)	Not approved to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) in combination with standard antiplatelet therapy
Complete response letter: more information required		
SABER-Bupivacaine	<i>Posidur</i> (DURECT Corp.)	Surgical site administration for postsurgical analgesia; more clinical trials will be required to assess the drug's safety.
Recommended for approval by an FDA advisory panel		
Ragweed pollen allergen extract tablet	<i>Ragwitek</i> (Merck)	Sublingual tablet for immunotherapy for the diagnosis of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis recommended for approval by the FDA's Allergenic Products Advisory Committee (6-2-1).
Recommended for NON-approval by an FDA advisory panel		
Cangrelor	(The Medicines Co.)	The FDA's Cardiovascular and Renal Advisory Committee recommended against approval of cangrelor for prevention of thrombotic events associated with coronary stenting (2-7) and for use of the drug in patients whose existing antiplatelet therapy is interrupted for surgery (0-9).
Nonsteroidal anti-inflammatory drugs	(various)	The FDA's Arthritis Advisory and Drug Safety and Risk Management Advisory Committee did not agree (16-9) with the data provided the Committee to support the claim that naproxen had a lower risk of heart attacks and stroke than similar nonsteroidal anti-inflammatory drugs.

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Table 3. Agents pending FDA approval: January 18, 2014 through February 16, 2014 (CONT.)

Generic name	Brand name (Company)	Indication and comments
Agents scheduled for review by an FDA advisory panel		
Dalbavancin	(Durata Therapeutics International)	Treatment of acute bacterial skin and skin structure infections.
Tedizolid phosphate	(Trius Therapeutics)	Treatment of acute bacterial skin and skin structure infections.

Table 4. New drug / biologics license applications filed by manufacturer: January 18, 2014 through February 16, 2014

Generic name Brand name (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Ledipasvir / sofosbuvir (Gilead Sciences)	Sofosbuvir	Treatment of chronic hepatitis C genotype 1 infection in adults	Non-structural-5A (NS5A) inhibitor / nucleotide analog polymerase inhibitor	Nausea, anemia, upper respiratory tract infection, and headache	Oral	Once daily oral regimen that is classified as “breakthrough therapy.”

Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a

Generic name Brand name (Company)	Warning
Azacitidine <i>Vidaza</i> (Celgene)	WARNINGS AND PRECAUTIONS Renal Abnormalities Deleted the statement, “Safety and effectiveness of <i>Vidaza</i> in patients with MDS and renal impairment have not been studied as these patients were excluded from the clinical trials.” USE IN SPECIFIC POPULATIONS Renal Impairment - new section added Severe renal impairment has no major effect on the pharmacokinetic exposure of azacitidine after single and multiple subcutaneous (SC) administrations. Therefore, azacitidine can be administered to subjects with renal impairment without initial dose adjustment. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289980.htm
Boceprevir <i>Victrelis</i> (Merck)	CONTRAINDICATIONS: Table 2 added alfuzosin, doxazosin, silodosin, and tamsulosin. DRUG INTERACTIONS Added calcium channel blockers, amlodipine, diltiazem, nisoldipine, and verapamil http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303600.htm
Doripenem <i>Doribax</i> (Shionogi)	WARNINGS AND PRECAUTIONS Increased Mortality in Ventilator-Associated Bacterial Pneumonia In a clinical trial of patients with ventilator-associated bacterial pneumonia comparing doripenem to imipenem, more subjects receiving doripenem died (23%; 31/135) compared to those receiving imipenem (16.7%; 22/132) based on 28-day all-cause mortality in the intent-to-treat population. Clinical response rates were also lower in the doripenem arm. Doripenem is not approved for the treatment of ventilator-associated bacterial pneumonia. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351550.htm

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Dronedaron hydrochloride <i>Multaq</i> (sanofi-aventis)	<p>WARNING AND PRECAUTIONS</p> <p>Renal Impairment and Failure</p> <p>Marked increase in serum creatinine, pre-renal azotemia, and acute renal failure, often in the setting of heart failure or hypovolemia, have been reported in patients taking <i>Multaq</i>. In most cases, these effects appear to be reversible upon drug discontinuation and with appropriate medical treatment. Monitor renal function periodically.</p> <p>Small increases in creatinine levels (about 0.1 mg/dL) following dronedarone treatment initiation have been shown to be a result of inhibition of creatinine’s tubular secretion. The elevation has a rapid onset, reaches a plateau after 7 days, and is reversible after discontinuation.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm243762.htm</p>
Fosphenytoin sodium <i>Cerebyx</i> (Pfizer)	<p>WARNINGS</p> <p>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including phenytoin and <i>Cerebyx</i>.</p> <p>PRECAUTIONS</p> <p>Drug Interactions: addition of tacrolimus and albendazole</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm283239.htm</p>
Lidocaine hydrochloride and dextrose 5% injection (Hospira)	<p>CONTRAINDICATIONS</p> <p>Lidocaine hydrochloride is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.</p> <p>Lidocaine should not be used in patients with Stokes-Adams syndrome, Wolff-Parkinson-White syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block.</p> <p>Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.</p> <p>WARNINGS</p> <p>Constant monitoring with an electrocardiograph is essential to the proper administration of lidocaine hydrochloride intravenously. It is mandatory to have emergency resuscitative equipment and drugs immediately available to manage adverse reactions involving cardiovascular, respiratory, or central nervous systems. Anaphylactic reactions may occur following administration of lidocaine hydrochloride. In the case of severe reaction, discontinue the use of the drug.</p> <p>PRECAUTIONS</p> <p>General</p> <p>Caution should be employed in the repeated use of lidocaine hydrochloride in patients with severe liver or renal disease because accumulation may occur and lead to toxic phenomena, since lidocaine hydrochloride is metabolized mainly in the liver and excreted by the kidneys. The drug should also be used with caution in patients with hypovolemia and shock and in all forms of heart block.</p> <p>In patients with sinus bradycardia or incomplete heart block, the administration of lidocaine hydrochloride intravenously for the elimination of ventricular ectopic beats without prior acceleration in heart rate (eg, by isoproterenol or by electric pacing) may promote more frequent and serious ventricular arrhythmias or complete heart block.</p> <p>Most potent anesthetic agents, local anesthetics of the amide type that includes lidocaine, and muscle relaxants of both depolarizing and nondepolarizing types have been associated with malignant hyperthermia.</p> <p>Care should be taken in the administration of intravenous fluids in patients with compromised myocardial function to avoid fluid overload or disturbances of serum electrolyte concentrations which might interfere with cardiac conduction or result in congestive heart failure.</p> <p>If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result. If administration is not controlled by a pumping device, refrain from applying excessive pressure (>300 mm Hg) causing distortion to the container such as wringing or twisting. Such handling could result in breakage of the container.</p>

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	<p>These solutions are intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours. Use only if solution is clear and container and seals are intact.</p> <p>Drug Interactions</p> <p>Added: potential interactions with cimetidine and amiodarone.</p> <p>ADVERSE REACTIONS</p> <p>Systemic reactions of the following types have been reported:</p> <p>Central Nervous System: Light-headedness; drowsiness; dizziness; apprehension; euphoria; tinnitus; blurred or double vision; vomiting; sensation of heat, cold, or numbness; twitching; tremors; convulsions; unconsciousness; respiratory depression and arrest.</p> <p>Cardiovascular System: Hypotension, cardiovascular arrest, and bradycardia, which may lead to cardiac arrest.</p> <p>Hematologic Effects: Methemoglobinemia.</p> <p>Allergic reactions, including anaphylactic reactions, may occur but are infrequent. There have been no reports of cross-sensitivity between lidocaine hydrochloride and procainamide or between lidocaine hydrochloride and quinidine.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342035.htm</p>
Losartan potassium <i>Cozaar</i>	<p>BOXED WARNING</p> <p>Warning: Fetal toxicity</p> <p>When pregnancy is detected, discontinue <i>Cozaar</i> as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.</p>
Losartan potassium / hydrochlorothiazide <i>Hyzaar</i> (Merck)	<p>WARNINGS</p> <p>Fetal Toxicity: Pregnancy Category D - extensive revision to this section</p> <p>PRECAUTIONS</p> <p>Pregnancy:</p> <p>Female patients of childbearing age should be told about the consequences of exposure to <i>Cozaar</i> during pregnancy. Discuss treatment options with women planning to become pregnant.</p> <p>Neonates with a history of in utero exposure to <i>Cozaar</i>: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm169666.htm</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm169677.htm</p>
Rivaroxaban <i>Xarelto</i> (Janssen Pharms)	<p>WARNINGS AND PRECAUTIONS</p> <p>Risk of Bleeding</p> <ul style="list-style-type: none"> Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. <p>Reversal of Anticoagulant Effect:</p> <ul style="list-style-type: none"> A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated. <p>Use with P-gp and Strong CYP3A4 Inhibitors or Inducers</p> <ul style="list-style-type: none"> Avoid concomitant use of <i>Xarelto</i> with combined P-gp and strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Avoid concomitant use of <i>Xarelto</i> with drugs that are combined P-gp and strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort). <p>Patients with Prosthetic Heart Valves</p> <ul style="list-style-type: none"> 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.

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	<p>Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy</p> <ul style="list-style-type: none"> Initiation of <i>Xarelto</i> is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367392.htm</p>
Sildenafil <i>Revatio</i> (Pfizer)	<p>WARNINGS AND PRECAUTIONS: Use of Sildenafil with Bosentan - section deleted</p> <p>USE IN SPECIFIC POPULATIONS</p> <p>Pregnancy - Pregnancy Category B: There are no adequate and well-controlled studies of sildenafil in pregnant women.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319416.htm</p>
Topiramate <i>Topamax</i> (Janssen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm195797.htm</p>

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