Current FDA-Related Drug Information

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

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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): December 19, 2013 through January 17, 2014

Coagulation Factor XIII A-subunit (Recombinant) – <i>Tretten</i> (Novo Nordisk)	
<i>Comparative agents:</i>	Plasma, cryoprecipitate, and factor XIII concentrates
<i>Indication:</i>	Prevention of bleeding in adults and children who have congenital factor XIII A-subunit deficiency
<i>Mechanism of action:</i>	Replacement clotting factor
<i>Common adverse effects:</i>	Headache, pain in the extremities, injection site pain
<i>Dosage form & strength:</i>	Injection (lyophilized powder)
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM379763.pdf
Dapagliflozin – <i>Farxiga</i> (Bristol-Myers Squibb & AstraZeneca)	
<i>Comparative agents:</i>	Canagliflozin
<i>Indication:</i>	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<i>Mechanism of action:</i>	Sodium-glucose co-transporter 2 (SGLT2) inhibitor that blocks the reabsorption of glucose by the kidney, increases glucose excretion, and lowers blood glucose levels
<i>Common adverse effects:</i>	Female genital mycotic infections, nasopharyngitis, and urinary tract infections
<i>Dosage form & strength:</i>	Tablet; 5 mg and 10 mg
<i>Product labeling:</i>	http://packageinserts.bms.com/pi/pi_farxiga.pdf

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Treprostinil – Orenitram (Supernus Pharmaceuticals)	
<i>Comparative agents:</i>	Treprostinil
<i>Indication:</i>	Treatment of pulmonary arterial hypertension in WHO Group I patients to improve exercise capacity
<i>Mechanism of action:</i>	Direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation
<i>Common adverse effects:</i>	Headache, nausea, and diarrhea
<i>Dosage form & strength:</i>	Tablet; 0.125 mg, 0.25 mg, 1 mg, and 2.5 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203496s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: December 19, 2013 through January 17, 2014

Generic name	Brand name (Company)	Indication and comments
New dosage forms/ strength/route of administration		
Diclofenac	<i>Pennsaid</i> (Mallinckrodt)	2% formulation for the treatment of pain associated with osteoarthritis of the knee
Raltegravir	<i>Isentress</i> (Merck)	New pediatric oral suspension formulation
Sapropterin dihydrochloride	<i>Kuvan</i> (BioMarin Pharm)	Powder for oral solution formulation.
New indications		
Trametinib plus Dabrafenib	<i>Mekinist</i> (GlaxoSmithKline) plus <i>Tafinlar</i> (GlaxoSmithKline)	Treatment of patients with advanced melanoma that is unresectable or metastatic

Table 3. Agents pending FDA approval: December 19, 2013 through January 17, 2014

Generic name	Brand name (Company)	Indication and comments
Complete response letter: more information required		
Ferumoxytol	<i>Feraheme</i> (AMAG Pharmaceuticals)	More data to expand its indication from chronic kidney disease to all adult iron deficiency anemia in patients who have failed or cannot tolerate oral iron treatment
Norethindrone	(Actavis)	Contraceptive patch applied once weekly; concern regarding the difference in size and formulation of the patch used in the clinical trials and the to-be-marketed patch
Delayed decision by the FDA		
Vedolizumab	(Takeda Pharmaceutical)	Prescription Drug User Fee Act Priority Review action date for the ulcerative colitis indications has been moved to May 20, 2014 to allow the FDA to review newly submitted information.

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Table 3. Agents pending FDA approval: December 19, 2013 through January 17, 2014 (CONT.)

Generic name	Brand name (Company)	Indication and comments
Recommended for approval by an FDA advisory panel		
Droxidopa	<i>Northera</i> (Chelsea Therapeutics)	Recommended for approval (16-1) by the FDA's Cardiovascular and Renal Drugs Advisory Committee for the treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta hydroxylase deficiency, and nondiabetic autonomic neuropathy.
Vorapaxar sulfate	<i>Zontivity</i> (Merck)	Recommended for approval (10-1) by the FDA's Cardiovascular and Renal Drugs Advisory Committee for the reduction of atherothrombotic events in patients with a history of myocardial infarction.
Recommended for NON-approval by an FDA advisory panel		
Alemtuzumab	<i>Lemtrada</i> (sanofi)	Potential benefits did not outweigh the risk of serious adverse effects associated with the treatment of relapsing remitting multiple sclerosis.
Rivaroxaban	<i>Xarelto</i> (Johnson & Johnson)	Not recommended for approval (10:0) by the FDA's Cardiovascular and Renal Drugs Advisory Committee to reduce the risk of thrombotic cardiovascular events in patients in the first 90 days after suffering acute coronary syndrome (ST elevation myocardial infarction, non-ST elevation myocardial infarction, or unstable angina).
Agents scheduled for review by an FDA advisory panel		
Cangrelor	(The Medicines Company)	Reduction of thrombotic cardiovascular events including stent thrombosis in patients with coronary artery disease undergoing percutaneous coronary intervention
Insulin human [rDNA origin] inhalation powder	<i>Afrezza</i> (MannKind Corporation)	Inhaled insulin for the treatment of diabetes mellitus
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
Serelaxin	(Novartis)	Improvement of the symptoms of acute heart failure through reduction of the rate of worsening of heart failure

Table 4. New drug / biologics license applications filed by manufacturer: December 19, 2013 through January 17, 2014

Generic name <i>Brand name</i> (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Liraglutide (Novo Nordisk)	Liraglutide	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity, or who are overweight with comorbidities	Glucagon-like peptide-1 receptor agonist	Headache, nausea, diarrhea, urticaria	Oral	Alternative weight loss agent; most likely will have a different brand name if approved for this indication.
Peramivir (BioCryst Pharmaceuticals)	Oseltamivir, zanamivir	Treatment of adults with acute uncomplicated influenza	Neuraminidase inhibitors	Diarrhea, nausea, vomiting, and neutropenia	Intravenous	IV neuraminidase inhibitors
Tacrolimus <i>Envars</i> (Veloxis Pharmaceuticals)	Tacrolimus	Prevention of organ rejection in kidney transplant recipients	Inhibition of T-cell activation and induces immunosuppression	Nephrotoxicity, hypertension, hyperkalemia, headache, insomnia, tremor, paresthesias, dizziness, and infections, including bronchitis, herpes simplex, oral candidiasis, peritonitis, pharyngitis, pneumonia, rhinitis, sepsis, sinusitis, and urinary tract infection	Oral	Once-daily formulation
Testosterone <i>Rextoro</i> (Clarus Therapeutics)	Testosterone	Testosterone replacement therapy	Testosterone replacement	Gastrointestinal disturbances, decrease in HDL cholesterol, and increase in hematocrit and prostate-specific antigen	Oral	

Table 5. Supplemental applications filed by manufacturer: December 19, 2013 through January 17, 2014

Generic Name	Brand name (Company)	Comments
Apixaban	<i>Eliquis</i> (Bristol-Myers Squibb)	Reduction in the risk of recurrent deep vein thrombosis and pulmonary emboli

Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a

Generic Name Brand Name (Company)	Warning
Belimumab <i>Benlysta</i> (GlaxoSmithKline)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypersensitivity Reactions, Including Anaphylaxis</p> <ul style="list-style-type: none"> Acute hypersensitivity reactions, including anaphylaxis and death, have been reported in association with belimumab. These events generally occurred within hours of the infusion; however they may occur later. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema have been reported and typically occurred up to a week following the most recent infusion. Hypersensitivity, including serious reactions, has occurred in patients who had tolerated previously infusions of belimumab. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299628.htm</p>
Bevacizumab <i>Avastin</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> The risk of developing arterial thromboembolic events during therapy is increased in patients with a history of arterial thromboembolism, diabetes, or age greater than 65. <p>ADVERSE REACTIONS</p> <p>Clinical Trial Experience</p> <ul style="list-style-type: none"> 5.4% of patients receiving <i>Avastin</i> in combination with chemotherapy experienced grade ≥ 2 proteinuria. The grade ≥ 2 proteinuria resolved in 74.2% of patients. <i>Avastin</i> was re-initiated in 41.7% of patients and 47.8% experienced a second episode of grade ≥ 2 proteinuria. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275758.htm</p>
Carboprost tromethamine <i>Hemabate</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Hypersensitivity (including anaphylaxis and angioedema) to <i>Hemabate</i> sterile solution <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Hypersensitivity reactions (eg, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, angioedema). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm380783.htm</p>
Clopidogrel bisulfate <i>Plavix</i> (Bristol-Myers Squibb)	<p>WARNINGS AND PRECAUTIONS</p> <p>Cross-Reactivity among Thienopyridines</p> <ul style="list-style-type: none"> Hypersensitivity including rash, angioedema, or hematologic reaction have been reported in patients receiving <i>Plavix</i>, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Acquired hemophilia A, erythematous or exfoliative rash <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, therefore the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm225843.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Docetaxel <i>Taxotere</i> (sanofi-aventis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Eye Disorders</p> <ul style="list-style-type: none"> Cystoid macular edema (CME) has been reported in patients treated with <i>Taxotere</i>, as well as with other taxanes. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. If CME is diagnosed, <i>Taxotere</i> treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experiences</p> <ul style="list-style-type: none"> Cases of hyponatremia have been reported <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm212079.htm</p>
Dofetilide <i>Tikosyn</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Dolutegravir should not be used in patients on dofetilide. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm266132.htm</p>
Ipilimumab <i>Yervoy</i> (Bristol-Myers Squibb)	<p>WARNINGS AND PRECAUTIONS</p> <p>Concurrent Administration with Vemurafenib</p> <ul style="list-style-type: none"> Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent <i>Yervoy</i> (3 mg/kg) and vemurafenib (960 mg twice daily or 720 mg twice daily). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm328023.htm</p>
Natalizumab <i>Tysabri</i> (Biogen Idec)	<p>BOXED WARNING</p> <p>WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY</p> <ul style="list-style-type: none"> Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML). Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-John Cunningham virus (anti-JCV) antibodies. Health care professionals should monitor patients on natalizumab for any new sign or symptom that may be suggestive of PML. Natalizumab dosing should be withheld immediately at the first sign or symptom suggestive of PML. Because of the risk of PML, natalizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH Prescribing Program. <p>WARNINGS AND PRECAUTIONS</p> <p>Progressive Multifocal Leukoencephalopathy</p> <ul style="list-style-type: none"> PML, an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised and that usually leads to death or severe disability, has occurred in patients who have received <i>Tysabri</i>... <p>Herpes Encephalitis and Meningitis</p> <ul style="list-style-type: none"> Natalizumab increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving natalizumab. Laboratory confirmation in those cases was based on positive PCR for viral DNA in the cerebrospinal fluid. The duration of treatment with natalizumab prior to onset ranged from a few months to several years. Monitor patients receiving natalizumab for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, natalizumab should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
	<p>Hepatotoxicity</p> <ul style="list-style-type: none"> Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with natalizumab in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as 6 days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon rechallenge, providing evidence that natalizumab caused the injury. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Natalizumab should be discontinued in patients with jaundice or other evidence of significant liver injury (eg, laboratory evidence). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm355780.htm</p>
Ponatinib <i>Iclusig</i> (ARIAD Pharmaceuticals)	<p>BOXED WARNING WARNING: VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY</p> <p>Vascular Occlusion</p> <ul style="list-style-type: none"> Arterial and venous thrombosis and occlusions have occurred in at least 27% of treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion. <p>WARNINGS AND PRECAUTIONS</p> <p>Vascular Occlusion</p> <ul style="list-style-type: none"> Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures, have occurred. <p>Heart Failure</p> <ul style="list-style-type: none"> Fatal and serious heart failure or left ventricular dysfunction occurred in 5% of treated patients. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of ponatinib. Consider discontinuation of ponatinib in patients who develop serious heart failure <p>Hypertension</p> <ul style="list-style-type: none"> Treatment-emergent hypertension occurred in 67% of patients, including reports of hypertensive crisis. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. <p>Neuropathy</p> <ul style="list-style-type: none"> Peripheral and cranial neuropathy occurred in treated patients; 13% experienced a peripheral neuropathy event of any grade and cranial neuropathy occurred in 1%. <p>Ocular Toxicity</p> <ul style="list-style-type: none"> Serious ocular toxicities leading to blindness or blurred vision have occurred in treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 3% of treated patients. Conjunctival or corneal irritation, dry eye, or eye pain occurred in 13% of patients. Visual blurring occurred in 6% of the patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Comprehensive eye exams should be conducted at baseline and periodically during treatment. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm380782.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Ranolazine <i>Ranexa</i> (GILEAD)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min) while taking ranolazine. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Marked and progressive increases in serum creatinine, associated with increases in BUN or potassium, indicating acute renal failure, have been reported after initiation of ranolazine in patients with severe renal impairment. <p>USE IN SPECIFIC POPULATIONS</p> <p>Use in Patients with Renal Impairment</p> <ul style="list-style-type: none"> Monitor renal function periodically in patients with moderate to severe renal impairment. Discontinue ranolazine if acute renal failure develops. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm229433.htm</p>
Sodium phosphate: OTC for constipation (various)	<p>Using more than one dose in 24 hours of over-the-counter (OTC) sodium phosphate drugs to treat constipation can cause rare but serious harm to the kidneys and heart and even death. Reports included episodes of severe dehydration and changes in the levels of serum electrolytes, resulting in serious adverse effects on organs, such as the kidneys and heart, and in some cases resulting in death. Individuals that may be at higher risk for potential adverse events include young children; individuals older than 55 years; patients who are dehydrated; patients with kidney disease, bowel obstruction, or inflammation of the bowel; and patients who are using medications that may affect kidney function (eg, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal antiinflammatory drugs).</p> <p>Caregivers should not give the oral products to children 5 years and younger without first discussing with a health care professional. Health care professionals should use caution when recommending an oral dose of these products for children 5 years and younger. The rectal form of these products should never be given to children younger than 2 years.</p> <p>http://www.fda.gov/Drugs/DrugSafety/ucm380757.htm</p>

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