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): November 19, 2013 through December 18, 2013

Simeprevir – Olysio (Johnson & Johnson)

<i>Comparative agents:</i>	Boceprevir, sofosbuvir, telaprevir
<i>Indication:</i>	Treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen (peginterferon alfa and ribavirin); efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis).
<i>Mechanism of action:</i>	Hepatitis C virus (HCV) NS3/4A protease inhibitor
<i>Common adverse effects:</i>	Rash (including photosensitivity), pruritus and nausea
<i>Dosage form & strength:</i>	Capsule; 150 mg
<i>Product labeling:</i>	http://www.olsio.com/shared/product/olsio/prescribing-information.pdf

Sofosbuvir – Sovaldi (Gilead Sciences)

<i>Comparative agents:</i>	Boceprevir, simeprevir, telaprevir
<i>Indication:</i>	Treatment of CHC as a component of a combination antiviral treatment regimen; efficacy has been established in subjects with HCV genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 coinfection.
<i>Mechanism of action:</i>	NS5B polymerase inhibitor
<i>Common adverse effects:</i>	Fatigue, headache, nausea, insomnia, and anemia; some adverse events may be caused by the concurrent use with ribavirin or peginterferon.
<i>Dosage form & strength:</i>	Tablets; 400 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf

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Table 1. New drugs approved by the US Food and Drug Administration (FDA): November 19, 2013 through December 18, 2013 (CONT.)

Sucroferric oxyhydroxide – Velphoro (Fresenius Medical Care North America)	
<i>Comparative agents:</i>	Calcium carbonate, sevelamer
<i>Indication:</i>	Treatment of hyperphosphatemia in chronic kidney disease patients on dialysis
<i>Mechanism of action:</i>	Iron-based phosphate binder; binds dietary phosphate in the gastrointestinal tract
<i>Common adverse effects:</i>	Discolored feces, diarrhea
<i>Dosage form & strength:</i>	Chewable tablet; 500 mg
<i>Product labeling:</i>	https://www.velphoro.us/downloads/prescribing-information.pdf
Umeclidinium/vilanterol – Anoro Ellipta (GlaxoSmithKline)	
<i>Comparative agents:</i>	Inhaled anticholinergic and long-acting bronchodilators
<i>Indication:</i>	Long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema
<i>Mechanism of action:</i>	Anticholinergic and beta2-agonist bronchodilator
<i>Common adverse effects:</i>	Pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain
<i>Dosage form & strength:</i>	Inhalation powder; 62.5 mcg umeclidinium and 25 mcg vilanterol
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203975s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: November 19, 2013 through December 18, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/ route of administration		
Polidocanol	<i>Varithena</i> (BTG)	Injectable form formulation for the treatment of incompetent veins and visible varicosities of the great saphenous vein system
Posaconazole	<i>Noxafil</i> (Merck)	Delayed-release tablet (100 mg) formulation; previous only available as a suspension
New indications		
Collagenase Clostridium histolyticum	<i>Xiaflex</i> (Auxilium Pharmaceuticals)	Treatment of Peyronie's disease
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate	<i>Complera</i> (Gilead)	Single-tablet HIV-1 regimen for use in certain virologically suppressed adult patients on a stable antiretroviral regimen in order to replace their current antiretroviral treatment regimen
Sorafenib	<i>Nexavar</i> (Pfizer)	Treatment of locally recurrent or late-stage (metastatic), progressive, differentiated, thyroid carcinoma refractory to radioactive iodine treatment. Previous indications included treatment of renal cell carcinoma and hepatocellular carcinoma.

Table 3. Agents pending FDA approval: November 19, 2013 through December 18, 2013

Generic name	Brand name (Company)	Indication and comments
Delayed decision by the FDA		
Recombinant factor IX Fc fusion protein	<i>Alprolix</i> (Biogen Idec)	Treatment of hemophilia B
Recommended for approval by an FDA advisory panel		
Elosulfase alfa	<i>Vimizim</i> BioMarin	Treatment of Morquio A syndrome (mucopolysaccharidosis type IVA)
Grass allergy immunotherapy tablet (5 grass mixed pollens allergen extract from sweet vernal, orchard, perennial rye, timothy, and Kentucky bluegrass)	<i>Oralir</i> (Staffergenes)	Treatment of grass pollen allergy
Metreleptin	(Bristol-Myers Squibb / AstraZeneca)	Treating children and adults with generalized lipodystrophy
Vedolizumab	(Takeda)	Treatment of adults with moderately to severely active ulcerative colitis and Crohn's disease

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

Generic name Brand name (Company)	Warning
Alendronate sodium, cholecalciferol <i>Fosamax Plus D</i> (Merck)	<p>USE IN SPECIFIC POPULATIONS</p> <p>Pregnancy</p> <ul style="list-style-type: none"> There are no studies in pregnant women. <i>Fosamax Plus D</i> should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus. <p>Renal Impairment</p> <ul style="list-style-type: none"> <i>Fosamax Plus D</i> is not recommended for patients with creatinine clearance less than 35 mL/min. No dosage adjustment is necessary in patients with creatinine clearance values between 35 and 60 mL/min. <p>Hepatic Impairment</p> <ul style="list-style-type: none"> Alendronate sodium: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic impairment. No dosage adjustment is necessary <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208690.htm</p>
Aliskiren-containing products <i>Amturnide, Tekamlo, Tekturna, Tekturna HCT</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypotension</p> <ul style="list-style-type: none"> Symptomatic hypotension may occur after initiation of treatment with aliskiren in patients with marked volume depletion, patients with salt depletion, or with combined use of aliskiren and other agents acting on the renin-angiotensin-aldosterone system. The volume or salt depletion should be corrected prior to administration of aliskiren, or the treatment should start under close medical supervision. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm279774.htm</p>
Atorvastatin, amlodipine <i>Caduet</i> (Pfizer)	<p>USE IN SPECIAL POPULATIONS</p> <ul style="list-style-type: none"> Amlodipine: There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208616.htm</p>

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

Generic name Brand name (Company)	Warning
Chloroquine phosphate <i>Aralen</i> (sanofi-aventis)	<p>WARNINGS</p> <ul style="list-style-type: none"> Retinopathy/maculopathy as well as macular degeneration have been reported and irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy. Retinopathy has been reported to be dose related. Risk factors for the development of retinopathy include age, duration of treatment, and high daily and/or cumulated doses. <p>ADVERSE REACTIONS</p> <p>Special Senses – Ocular</p> <ul style="list-style-type: none"> Maculopathy and macular degeneration have been reported and may be irreversible. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377132.htm</p>
Clobazam <i>Onfi</i> (Lundbeck)	<p>Rare but serious skin reactions, called Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur at any time during clobazam treatment.</p> <p>http://www.fda.gov/downloads/Drugs/DrugSafety/UCM377282.pdf</p>
Crizotinib <i>Xalkori</i> (Pfizer)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hepatotoxicity</p> <ul style="list-style-type: none"> Drug-induced hepatotoxicity with fatal outcome occurred in 2 (0.2%) of the 1,225 patients treated with <i>Xalkori</i> across 3 main clinical trials. <p>Interstitial Lung Disease (Pneumonitis)</p> <ul style="list-style-type: none"> Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with <i>Xalkori</i>. <p>QT Interval Prolongation</p> <ul style="list-style-type: none"> QTc prolongation can occur in patients treated with <i>Xalkori</i>. <p>Bradycardia</p> <ul style="list-style-type: none"> Symptomatic bradycardia can occur in patients receiving <i>Xalkori</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295722.htm</p>
Golimumab <i>Simponi</i> (Janssen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Tuberculosis</p> <ul style="list-style-type: none"> Cases of active tuberculosis have occurred in patients treated with <i>Simponi</i> during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection. <p>Vaccinations/Therapeutic Infectious Agents</p> <ul style="list-style-type: none"> Live Vaccines: Patients treated with <i>Simponi</i> may receive vaccinations, except for live vaccines. In patients receiving anti-TNF therapy, limited data are available on the response to live vaccination, or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. Therapeutic Infectious Agents: Other uses of therapeutic infectious agents such as live attenuated bacteria (eg, BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with <i>Simponi</i>. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease Skin and subcutaneous tissue disorders: Skin exfoliation, rash <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351838.htm</p>

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

Generic name Brand name (Company)	Warning
Lansoprazole, amoxicillin, clarithromycin <i>Prevpac</i> (Takeda Pharmaceuticals America)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> History of severe hypersensitivity reactions (eg, anaphylaxis or Stevens-Johnson syndrome [SJS]) to amoxicillin or other beta-lactam antibiotics (eg, penicillins and cephalosporins) is a contraindication. Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes. Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis. <p>WARNINGS</p> <p>Acute Hypersensitivity Reactions</p> <ul style="list-style-type: none"> In the event of severe acute hypersensitivity reactions, such as anaphylaxis, SJS, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and Henoch-Schonlein purpura, <i>Prevpac</i> should be discontinued immediately and appropriate treatment should be urgently initiated. <p>QT Prolongation</p> <ul style="list-style-type: none"> Clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia <p>Gastric Malignancy</p> <ul style="list-style-type: none"> Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy. <p>Oral Hypoglycemic Agents/Insulin</p> <ul style="list-style-type: none"> The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. <p>Oral Anticoagulants</p> <ul style="list-style-type: none"> There is a risk of serious hemorrhage and significant elevations in international normalized ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently. <p>HMG-CoA Reductase Inhibitors (statins)</p> <ul style="list-style-type: none"> Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4, and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. <p>Concomitant Use of <i>Prevpac</i> with Methotrexate</p> <ul style="list-style-type: none"> Literature suggests that concomitant use of proton pump inhibitors (PPI) with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of <i>Prevpac</i> may be considered in some patients. In addition, published observational studies suggest that PPI therapy may be associated with an increased risk of <i>Clostridium difficile</i>-associated disease (CDAD), especially in hospitalized patients. <p>Adverse Reactions With Long-Term PPI Use</p> <ul style="list-style-type: none"> Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377161.htm</p>

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

Generic name Brand name (Company)	Warning
Lenalidomide <i>Revlimid</i> (Celgene Corporation)	WARNINGS AND PRECAUTIONS <ul style="list-style-type: none"> Increased mortality in patients with chronic lymphocytic leukemia http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299519.htm
Lisinopril <i>Zestril</i> (AstraZeneca)	CONTRAINDICATIONS <ul style="list-style-type: none"> Do not co-administer aliskiren with lisinopril in patients with diabetes. ADVERSE REACTIONS Nervous System/Psychiatric <ul style="list-style-type: none"> Hallucinations http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm165413.htm
Lisinopril, hydrochlorothiazide <i>Zestoretic</i> (AstraZeneca)	CONTRAINDICATIONS <ul style="list-style-type: none"> Do not co-administer aliskiren with lisinopril and hydrochlorothiazide in patients with diabetes. ADVERSE REACTIONS Nervous System/Psychiatric <ul style="list-style-type: none"> Hallucinations http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm165414.htm
Methylphenidate (various)	In rare instances, it can cause prolonged and sometimes painful erections known as priapism. http://www.fda.gov/Drugs/DrugSafety/ucm375796.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
Mitotane <i>Lysodren</i> (Bristol-Myers Squibb)	WARNINGS <ul style="list-style-type: none"> Literature reports suggest that mitotane plasma concentrations exceeding 20 mcg/mL are associated with a greater incidence of high-grade central nervous system toxicity. Since <i>Lysodren</i> increases hormone binding proteins, measurement of free cortisol and corticotropin (ACTH) levels may be useful in achieving optimal steroid replacement. PRECAUTIONS General <ul style="list-style-type: none"> Prolonged bleeding time has been reported in patients treated with <i>Lysodren</i>. Consider this possibility prior to any surgical intervention. Drug Interactions <ul style="list-style-type: none"> <i>Lysodren</i> is a strong inducer of cytochrome P-450 3A4 (CYP3A4). Monitor patients for a change in dosage requirements for the concomitant drug when administering <i>Lysodren</i> to patients receiving drugs that are substrates of CYP3A4. Pregnancy: Pregnancy Category D <ul style="list-style-type: none"> <i>Lysodren</i> can cause fetal harm when administered to a pregnant woman. Nursing Mothers <ul style="list-style-type: none"> Mitotane has been detected in breast milk. Because of the potential for serious adverse reactions in nursing infants from mitotane, advise women to discontinue nursing during <i>Lysodren</i> therapy and after treatment discontinuation for as long as mitotane plasma levels are detectable. ADVERSE REACTIONS <ul style="list-style-type: none"> Infrequently occurring side effects involve the eye (visual blurring, diplopia, lens opacity, toxic retinopathy); the genitourinary system (hematuria, hemorrhagic cystitis, and albuminuria); cardiovascular system (hypertension, orthostatic hypotension, and flushing); and some miscellaneous effects including generalized aching, hyperpyrexia, and lowered protein-bound iodine. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377162.htm

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

Generic name Brand name (Company)	Warning
Pioglitazone hydrochloride <i>Actos</i> (Takeda Pharmaceuticals)	USE IN SPECIFIC POPULATIONS Pediatric Use <ul style="list-style-type: none"> <i>Actos</i> is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377135.htm
Pioglitazone hydrochloride plus glimepiride <i>Duetact</i> (Takeda Pharmaceuticals)	USE IN SPECIFIC POPULATIONS Pediatric Use <ul style="list-style-type: none"> <i>Duetact</i> is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumor. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm230389.htm
Pioglitazone hydrochloride, metformin hydrochloride <i>Actoplus Met XR</i> (Takeda Pharmaceuticals)	USE IN SPECIFIC POPULATIONS Pediatric Use <ul style="list-style-type: none"> <i>Actoplus Met XR</i> is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377137.htm
Posaconazole <i>Noxafil</i> (Merck)	WARNINGS AND PRECAUTIONS <ul style="list-style-type: none"> Calcineurin-Inhibitor Drug Interactions: Concomitant administration of <i>Noxafil</i> with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377313.htm
Ruxolitinib <i>Jakafi</i> (Incyte Corporation)	WARNINGS AND PRECAUTIONS Risk of Infection <ul style="list-style-type: none"> Serious bacterial, mycobacterial, fungal, and viral infections may occur. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377314.htm
Sorafenib <i>Nexavar</i> (Bayer HealthCare Pharmaceuticals)	WARNINGS AND PRECAUTIONS <ul style="list-style-type: none"> Impairment of Thyroid Stimulating Hormone (TSH) Suppression in DTC: <i>Nexavar</i> impairs exogenous thyroid suppression. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021923s016lbl.pdf

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