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): July 18, 2013 through August 26, 2013

Brimonidine – Mirvaso (Galderma)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Topical treatment of the facial erythema (redness) of rosacea in adults 18 years of age or older
<i>Mechanism of action:</i>	Selective alpha-2 adrenergic agonist
<i>Common adverse effects:</i>	Erythema, flushing, skin-burning sensation, and contact dermatitis
<i>Dosage form & strength:</i>	Gel; 0.33%
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204708lbl.pdf
Dolutegravir – Tivicay (ViiV Healthcare)	
<i>Comparative agents:</i>	Elvitegravir, Raltegravir
<i>Indication:</i>	Human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg
<i>Mechanism of action:</i>	Inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration that is essential for the HIV replication cycle
<i>Common adverse effects:</i>	Insomnia and headache
<i>Dosage form & strength:</i>	Tablet; 50 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf
Levomilnacipran – Fetzima (Forest Laboratories)	
<i>Comparative agents:</i>	Milnacipran
<i>Indication:</i>	Treatment of major depression
<i>Mechanism of action:</i>	Serotonin and norepinephrine reuptake inhibitor (SNRI)
<i>Common adverse effects:</i>	Nausea, vomiting, constipation, tachycardia, hyperhidrosis, erectile dysfunction, palpitations
<i>Dosage form & strength:</i>	Capsules; 20 mg, 40 mg, 80 mg, 120 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204168s000lbl.pdf

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Table 1. New drugs approved by the US Food and Drug Administration (FDA): July 18, 2013 through August 26, 2013 (CONT.)

Mechlorethamine – Valchlor gel (Ceptaris)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of Stage 1A and 1B mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy
<i>Mechanism of action:</i>	Nitrogen mustard compound that works as an alkylating agent to inhibit rapidly proliferating cells
<i>Common adverse effects:</i>	Dermatitis, pruritus, bacterial skin infection, skin ulceration or blistering, and hyperpigmentation
<i>Dosage form & strength:</i>	Gel: 0.016% w/w
<i>Product labeling:</i>	http://valchlor.com/Valchlor.pdf
Norethindrone acetate / ethinyl estradiol; ethinyl estradiol; ferrous fumarate – LO Minastrin FE (Warner Chilcott)	
<i>Comparative agents:</i>	Norethindrone / ethinyl estradiol
<i>Indication:</i>	Prevention of pregnancy
<i>Mechanism of action:</i>	Hormonal contraceptive
<i>Common adverse effects:</i>	Nausea/vomiting, headache, bleeding irregularities, dysmenorrhea, weight change, breast tenderness, acne, abdominal pain, anxiety and depression
<i>Dosage form & strength:</i>	24 blue, mint-flavored, chewable tablets, each containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol; 2 white tablets each containing 10 mcg ethinyl estradiol; and 2 brown tablets each containing 75 mg ferrous fumarate
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204654s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: July 18, 2013 through August 26, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/route of administration		
Atorvastatin/Ezetimibe	<i>Liptruzet</i> (Merck)	New combination product available in 10/10, 20/10, 40/10, and 80/10 (mg/mg) atorvastatin/ezetimibe strength tablets
Golimumab	<i>Simponi Aria</i> (Janssen Biotech)	The prefilled syringe and <i>SmartJect</i> autoinjector formulations are used for subcutaneous injection that are administered once a month in the treatment of rheumatoid arthritis. The new infusion formulation can be given as a 30-minute infusion at week 0 and week 4 and then every 8 weeks thereafter.
Insulin pen for children	(Novo Nordisk)	New insulin pen that has half-unit dosing and a memory function that records the dose and time since the last injection
Tacrolimus	<i>Astagraf XL</i> (Astellas)	Extended-release capsule for the prophylaxis of organ rejection in adult kidney transplant recipients used with mycophenolate mofetil and corticosteroids, with or without basiliximab induction
Topiramate	<i>Trokendi XR</i> (Supernus)	Once-daily, extended-release formulation of topiramate for the treatment of epilepsy
New indications		
Quadrivalent meningococcal vaccine	<i>Menveo</i> (Novartis)	Infants and toddlers from 2 months to age 1 were added to the approved patient population for this meningococcal vaccine.

Table 3. Agents pending FDA approval: July 18, 2013 through August 26, 2013

Generic name <i>Brand name</i> (Company)		Indication and comments
Delayed decision by the FDA		
Albiglutide	(GlaxoSmithKline)	Three month extension; new Prescription Drug User Fee Act (PDUFA) date will be April 15, 2014.
Recommended for approval by an FDA advisory panel		
Certolizumab	<i>Cimzia</i> (UCB)	Vote of 7 yes, 6 no, and 1 abstention for approval as a treatment of active axial spondyloarthritis, ankylosing spondylitis, and nonradiographic axial spondyloarthritis
Riociguat	<i>Adempas</i> (Bayer HealthCare)	Treatment of pulmonary arterial hypertension of World Health Organization (WHO) Group 1; treatment of chronic thromboembolic pulmonary hypertension of WHO Group 4
Triamcinolone acetonide	<i>Nasacort AQ</i> nasal spray (Sanofi-Aventis)	Recommended for prescription to over-the-counter transfer.
Recommended for NON-approval by an FDA advisory panel		
Adalimumab	<i>Humira</i> (AbbVie)	12 to 1 vote against approval for the treatment of nonradiographic axial spondyloarthritis
Tolvaptan	<i>Samsca</i> (Otsuka Pharmaceuticals)	Not approved for the treatment of autosomal dominant polycystic kidney disease
Agents scheduled for review by an FDA advisory panel		
Umeclidinium bromide/ vilanterol	<i>Anoro Ellipta</i> (GlaxoSmithKline)	Once daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema

Table 4. New drug/biologics license applications filed by manufacturer: July 18, 2013 through August 26, 2013

Generic name <i>Brand name</i> (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route
Ferric citrate <i>Zerenex</i> (Keryx Biopharmaceuticals)	Calcium acetate; ferric ammonium citrate; sevelamer	Treat hyperphosphatemia in patients with chronic kidney disease	Phosphate binder: binds with phosphate and forms a nonabsorbable complex	Black stools	Oral

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

Generic name Brand name (Company)	Warning
Acetaminophen (various)	Serious skin reactions added to the warning section of the product labeling: Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm363519.htm?source=govdelivery
Anagrelide <i>Agrilyn</i> (Shire)	WARNINGS Cardiovascular Torsades de pointes and ventricular tachycardia have been reported with anagrelide treatment. Obtain a pretreatment cardiovascular examination, including an ECG in all patients. During treatment with anagrelide, monitor patients for cardiovascular effects and evaluate as necessary. Anagrelide is a phosphodiesterase 3 (PDE3) inhibitor and may cause vasodilation, tachycardia, palpitations, and congestive heart failure. Other drugs that inhibit PDE3 have caused decreased survival when compared with placebo in patients with Class III-IV congestive heart failure. In patients with cardiac disease, use <i>Agrilyn</i> only when the benefits outweigh the risks. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm175918.htm
Asparaginase <i>Elspar</i> (Lundbeck)	WARNINGS AND PRECAUTIONS Glucose Intolerance: Glucose intolerance can occur in patients receiving asparaginase. In some cases, glucose intolerance is irreversible. Cases of diabetic ketoacidosis have been reported. Neurotoxicity: Patients treated with asparaginase, in a combination with other chemotherapeutic agents, have been reported to develop posterior reversible encephalopathy syndrome (PRES). PRES is a neurological disorder with clinical symptoms of headache, seizures, visual disturbances, altered mental status, and hypertension. Symptoms can be nonspecific, and diagnosis requires confirmation by radiological procedures. Interrupt use of <i>Elspar</i> if PRES is suspected or diagnosed. Control blood pressure promptly and monitor closely for seizure activity. Risk of Medication Errors: Medication errors involving <i>Elspar</i> have occurred. In particular, different formulations and routes of administration (intramuscular and intravenous) of asparaginase have been interchanged inappropriately, which may result in subtherapeutic blood levels of asparaginase or additional toxicity related to an overdose. Confirm the formulation of asparaginase prior to administration. Do not interchange <i>Elspar</i> with <i>Erwinaze</i> . http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm364150.htm
Denosumab <i>Prolia</i> (Amgen)	CONTRAINDICATIONS Hypersensitivity: Denosumab is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling, and urticaria. WARNINGS AND PRECAUTIONS Hypersensitivity: Clinically significant hypersensitivity including anaphylaxis has been reported with denosumab. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm307218.htm
Fluoroquinolones (Various)	The risk of peripheral neuropathy occurs only with fluoroquinolones that are taken by mouth or by injection. Topical formulations of fluoroquinolones, applied to the ears or eyes, have not been associated with this adverse reaction. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm365302.htm?source=govdelivery

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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
Ketoconazole <i>Nizoral</i> (Ortho McNeil Janssen)	Warning strengthened regarding severe liver injuries and adrenal gland problems and addition of a new medication guide to address these safety issues. Ketoconazole oral tablets should not be a first-line treatment for any fungal infection; it should be used for the treatment of endemic mycoses, only when alternative antifungal therapies are not available or tolerated. http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm
Mefloquine hydrochloride (Various)	Strengthened and updated warnings regarding neurologic and psychiatric side effects associated with this antimalarial drug. Patient medication guide was changed and needs to be dispensed with each prescription; it will include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations. http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm?source=govdelivery
Mometasone furoate / formoterol fumarate <i>Dulera</i> (Merck)	WARNINGS AND PRECAUTIONS Coexisting Conditions: <i>Dulera</i> , like other medications containing sympathomimetic amines, should be used with caution in patients with aneurysm, pheochromocytoma, etc. DRUG INTERACTIONS Halogenated Hydrocarbons: There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons. Postmarketing Experience: Cardiac arrhythmias, eg, atrial fibrillation, ventricular extrasystoles, tachyarrhythmia http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319217.htm
Naltrexone <i>Vivitrol</i> (Alkermes)	WARNINGS AND PRECAUTIONS Vulnerability to Opioid Overdose: Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after naltrexone treatment is discontinued, especially at the end of a dosing interval (ie, near the end of the month that <i>Vivitrol</i> was administered), or after a dose of <i>Vivitrol</i> is missed. It is important that patients inform family members and the people closest to the patient of this increased sensitivity to opioids and the risk of overdose. Injection Site Reactions: For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering health care provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1.5-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. Precipitation of Opioid Withdrawal: The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Review of postmarketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission and, in some cases, management in the intensive care unit. Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction were observed in association with <i>Vivitrol</i> exposure during the clinical development program and in the post-marketing period. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208449.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
Silodosin <i>Rapaflo</i> (Watson Pharmaceuticals)	<p>CONTRAINDICATIONS Patients with a history of hypersensitivity to silodosin or any of the ingredients of <i>Rapaflo</i></p> <p>ADVERSE REACTIONS Postmarketing Experience</p> <ul style="list-style-type: none"> • Skin rash, pruritis, and urticaria • Immune system disorders: allergic-type reactions, not limited to skin reactions, including swollen tongue and pharyngeal edema resulting in serious outcomes <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm207403.htm</p>
Sulfamethoxazole/ Trimethoprim (Various)	<p>WARNINGS Embryofetal Toxicity</p> <ul style="list-style-type: none"> • Severe and symptomatic hyponatremia can occur in patients receiving sulfamethoxazole/trimethoprim, particularly for the treatment of <i>P. jiroveci</i> pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complication. Some epidemiologic studies suggest that exposure to sulfamethoxazole/trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular malformations, urinary tract defects, oral clefts, and club foot. • If sulfamethoxazole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the fetus. <p>PRECAUTIONS Electrolyte Abnormalities: Severe and symptomatic hyponatremia can occur in patients treated with sulfamethoxazole/trimethoprim, particularly for the treatment of <i>P. jiroveci</i> pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications.</p> <p>ADVERSE REACTIONS Metabolic and Nutritional: hyponatremia</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319394.htm</p>
Sulfasalazine <i>Azulfidine EN</i> (Pfizer)	<p>WARNINGS</p> <ul style="list-style-type: none"> • Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of sulfasalazine. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Sulfasalazine should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. • Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking various drugs including sulfasalazine. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Sulfasalazine should be discontinued if an alternative etiology for the signs or symptoms cannot be established. <p>PRECAUTIONS Pregnancy: There have been reports of babies with neural tube defects born to mothers who were exposed to sulfasalazine during pregnancy, although the role of sulfasalazine in these defects has not been established. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm363979.htm</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
Tapentadol <i>Nucynta</i> (Janssen Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Patients with significant respiratory depression; acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment; known or suspected paralytic ileus; or hypersensitivity (eg, anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product <p>WARNINGS AND PRECAUTIONS</p> <p>Abuse Potential: Tapentadol, an opioid agonist and a Schedule II controlled substance, can be abused in a manner similar to other opioid agonists legal or illicit. Consider these risks when prescribing or dispensing in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.</p> <p>Life Threatening Respiratory Depression: Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status.</p> <p>Accidental Exposure: Accidental ingestion of tapentadol, especially in children, can result in a fatal overdose of tapentadol.</p> <p>Interactions with Alcohol, Other Opioids, and Drugs of Abuse: Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products containing alcohol, other opioids, or drugs of abuse while on tapentadol therapy.</p> <p>Elderly, Cachectic, and Debilitated Patients: Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.</p> <p>Use in Patients with Chronic Pulmonary Disease: Monitor for respiratory depression those patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercarbia, or preexisting respiratory depression, as in these patients, even at usual therapeutic doses.</p> <p>Hypotensive Effect: Tapentadol may cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs.</p> <p>Use in Patients with Head Injury or Increased Intracranial Pressure: Monitor patients taking tapentadol who may be susceptible to the intracranial effects of CO₂ retention (eg, those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression.</p> <p>Seizures: Tapentadol may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings.</p> <p>Serotonin Syndrome Risk: Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs.</p> <p>Driving and Operating Heavy Machinery: May impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.</p> <p>Renal Impairment: Use in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm233891.htm</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
Valproic acid; divalproex sodium; and valproate sodium All formulations (Various)	<p>BOXED WARNING</p> <p>Hepatotoxicity: Patients with Mitochondrial Disease: There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA polymerase γ (POLG) gene (eg, Alpers-Huttenlocher Syndrome). Valproate is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and in children under 2 years of age who are clinically suspected of having a mitochondrial disorder.</p> <p>CONTRAINDICATIONS</p> <p>Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; eg, Alpers-Huttenlocher Syndrome) and in children under 2 years of age who are suspected of having a POLG-related disorder.</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Hepatotoxicity: Patients with Known or Suspected Mitochondrial Disease: Valproate is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under 2 years of age who are clinically suspected of having a mitochondrial disorder. Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (eg, Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360487.htm</p>

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

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THERAPY CONSIDERATIONS

Metformin alone or in combination with lifestyle modification in the treatment and prevention of antipsychotic weight gain has been studied in several meta-analyses and controlled trials, suggesting a modest weight loss in most patients (2.93 to 5 kg).

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