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 bakerdan@wsu.edu.

Table 1. New drugs approved by the US Food and Drug Administration (FDA): April 16, 2013 through May 17, 2013

Brinzolamide / Brimonidine Tartrate – *Simbrinza* (Alcon)

<i>Comparative agents:</i>	Combination product of brinzolamide and brimonidine tartrate
<i>Indication:</i>	Reduction of elevated intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension
<i>Mechanism of action:</i>	Carbonic anhydrase inhibitor and alpha-2 adrenergic receptor agonist
<i>Common adverse effects:</i>	Blurred vision, eye irritation, dysgeusia, dry mouth, eye allergy
<i>Dosage form & strength:</i>	Ophthalmic suspension; 1%, 0.2%
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204251s000lbl.pdf

Cysteamine bitartrate – *Procysbi* (Raptor Pharmaceuticals)

<i>Comparative agents:</i>	Compounded cysteamine
<i>Indication:</i>	Management of nephropathic cystinosis in adults and children ages 6 years and older
<i>Mechanism of action:</i>	Replacement of missing component of lysosomes in the thiol-disulfide interchange reaction that converts cystine into cysteine and cysteine-cysteamine mixed disulfide
<i>Common adverse effects:</i>	Vomiting, abdominal pain/discomfort, headaches, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash
<i>Dosage form & strength:</i>	Delayed release capsule; 25 mg & 75 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203389s000lbl.pdf

Ezetimibe/Atorvastatin – *Liptruzet* (Merck)

<i>Comparative agents:</i>	Combination product of ezetimibe and atorvastatin
<i>Indication:</i>	Adjunctive therapy to diet to: • reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C and to increase HDL-C in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia. • reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments.

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Table 1. New drugs approved by the US Food and Drug Administration (FDA): April 16, 2013 through May 17, 2013 (CONT.)

<i>Mechanism of action:</i>	Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine and atorvastatin by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.
<i>Common adverse effects:</i>	Increased ALT, increased AST, musculoskeletal pain
<i>Dosage form & strength:</i>	Tablets; 10 mg/10 mg, 10 mg /20 mg, 10 mg /40 mg, 10 mg /80 mg
<i>Product labeling:</i>	http://www.merck.com/product/usa/pi_circulars/l/liptruzet/liptruzet_pi.pdf
Prothrombin complex concentrate – Kcentra (CSL Behring LLC)	
<i>Comparative agents:</i>	Vitamin K, <i>Bebulin VH</i> , <i>Proflnine SD</i> , Factor IX
<i>Indication:</i>	Urgent reversal of acquired coagulation factor deficiency induced by warfarin therapy in adult patients with acute major bleeding
<i>Mechanism of action:</i>	Vitamin K-dependent coagulation Factors II, VII, IX, and X, plus antithrombotic Protein C and Protein S, prepared from human plasma
<i>Common adverse effects:</i>	Headache, nausea, vomiting, arthralgia, and hypotension
<i>Dosage form & strength:</i>	Single-use vial/lyophilized concentrate of coagulation Factors II, VII, IX, and X, and antithrombotic Proteins C and S
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM350239.pdf
Radium Ra 223 dichloride – Xofigo (Algeta/Bayer)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease
<i>Mechanism of action:</i>	Alpha particle-emitting radioactive agent
<i>Common adverse effects:</i>	Nausea, diarrhea, vomiting, and peripheral edema
<i>Dosage form & strength:</i>	Injectable; 1,000 kBq/mL (27 microcurie/mL)
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf

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Table 2. New dosage forms and indications approved by the FDA: April 16, 2013 through May 17, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/ route of administration		
Nimodipine	<i>Nymalize</i> (Arbor Pharmaceuticals)	Oral solution of nimodipine (60 mg/mL) for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).
New indications		
Canakinumab	<i>Ilaris</i> (Novartis)	Treatment of active systemic juvenile idiopathic arthritis
Efavirenz	<i>SUSTIVA</i> (Bristol-Myers Squibb)	Approved as part of a regimen for HIV-1-infected infants as young as 3 months and weighing at least 3.5 kg.
Erlotinib	<i>Tarceva</i> (Astellas Pharma)	First-line treatment of metastatic non-small-cell lung cancer patients whose tumors have epidermal growth factor receptor exon 19 deletions or exon (L858R) substitution mutations
Golimumab	<i>Simponi</i> (Centocor Ortho Biotech)	Treatment of moderate to severe ulcerative colitis
Levonorgestrel	<i>Plan B One-Step</i> (Teva)	Use without a prescription by women 15 years of age and older; proof of age will be required and product cannot be sold in situations where age cannot be verified.
Lubiprostone	<i>Amitiza</i> (Sucampo)	Treatment of opioid-induced constipation in patients with chronic non-cancer pain

Table 3. Agents pending FDA approval: April 16, 2013 through May 17, 2013

Generic name	Brand name (Company)	Indication and comments
Complete response letter: more information required		
Buprenorphine	<i>Probuphine</i> (Titan Pharmaceuticals)	Subdermal implant for the maintenance treatment of opioid dependence in adult patients; more information required regarding efficacy, insertion and removal issues, and Risk Evaluation and Mitigation Strategy requirements.
Dihydroergotamine	<i>Levadex</i> (Allergan)	Treatment of acute migraines; more information requested regarding the delivery device and issues related to filling the delivery canisters

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Table 3. Agents pending FDA approval: April 16, 2013 through May 17, 2013 (CONT.)

Generic name	Brand name (Company)	Indication and comments
Delayed decision by the FDA		
Trametinib	(GlaxoSmithKline)	New PDUFA date is September 3, 2013; delayed based on time required to review additional manufacturing data submitted by the sponsor
Recommended for approval by an FDA advisory panel		
Fluticasone furoate /vilanterol	<i>BREO ELLIPTA</i> (GlaxoSmithKline)	Long-term maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease
Recommended for NON-approval by an FDA advisory panel		
Cobicistat	(Gilead Sciences)	Application to market this individual ingredient found in <i>Stribild</i> was denied based on deficiencies found at the manufacturing plant during the FDA inspection.
Elvitegravir	(Gilead Sciences)	Application to market this individual ingredient found in <i>Stribild</i> was denied based on deficiencies found at the manufacturing plant during the FDA inspection.
Levetiracetam	(Sun Pharma Advanced Research Company)	Concerns regarding the impact of food on the pharmacokinetics of the extended-release product
Tivozanib	(AVEO Pharmaceuticals)	Treatment of advanced renal cell carcinoma
FDA advisory panel - tie vote		
Testosterone	<i>Aveed</i> (Endo Health Solutions)	Long-acting injectable formulation designed to be given once every 12 weeks for the treatment of men with low testosterone levels
Agents scheduled for review by an FDA advisory panel		
Suvorexant	Merck	Treatment of insomnia characterized by difficulties with sleep onset and/or maintenance

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

Generic name Brand name (Company)	Warning
Bisphosphonate drug products – class labeling changes	Bisphosphonate drug <i>Actonel</i> (risedronate sodium) tablets <i>Actonel</i> with calcium (risedronate sodium with calcium carbonate) tablets <i>Atelvia</i> (risedronate sodium) delayed-release tablets <i>Binosto</i> (alendronate sodium) effervescent tablets for oral solution <i>Boniva</i> (ibandronate sodium) tablets <i>Didronel</i> (etidronate disodium) tablets <i>Fosamax</i> (alendronate sodium) tablets and oral solution <i>Fosamax Plus D</i> (alendronate sodium/cholecalciferol) tablets PRECAUTIONS Osteonecrosis of the Jaw - The risk of osteonecrosis of the jaw may increase with duration of exposure to bisphosphonates. ADVERSE REACTIONS Postmarketing Experience - Pulmonary - asthma exacerbations http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351740.htm
Candesartan cilexetil <i>Atacand</i> & <i>Atacand HCT</i> (Astra Zeneca)	CONTRAINDICATIONS - Candesartan is contraindicated in patients who are hypersensitive to candesartan. Do not administer aliskiren with candesartan in patients with diabetes. WARNINGS AND PRECAUTIONS Hypotension - Candesartan can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Impaired Renal Function - In the CHARM-Added program, where candesartan or placebo was given in addition to ACE inhibitors, the incidence of abnormal renal function (eg, creatinine increase) was 15% in patients treated with candesartan versus 9% in patients treated with placebo. Hyperkalemia - In the CHARM-Added program where candesartan or placebo was given in addition to ACE inhibitors, the incidence of hyperkalemia was 9.5% in patients treated with candesartan versus 3.5% in patients treated with placebo. ADVERSE REACTIONS Postmarketing Experience - Immunologic: Angioedema http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351996.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351976.htm

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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
Dabigatran etexilate mesylate <i>Pradaxa</i> (Boehringer Ingelheim Pharmaceuticals)	BOXED WARNING WARNING: Discontinuation of <i>Pradaxa</i> in patients without adequate continuous anticoagulation increases risk of stroke. WARNINGS AND PRECAUTIONS - Increased Risk of Stroke with Discontinuation of <i>Pradaxa</i> - Discontinuing <i>Pradaxa</i> in absence of adequate alternative anticoagulation increases the risk of thrombotic events. ADVERSE REACTIONS Postmarketing Experience - Thrombocytopenia http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250657.htm
Dutasteride/tamsulosin hydrochloride <i>Jalyn</i> (GlaxoSmithKline)	CONTRAINDICATIONS - Patients with previously demonstrated, clinically significant hypersensitivity (eg, serious skin reactions, angioedema, urticaria, pruritus, respiratory symptoms) to dutasteride, other 5 alpha-reductase inhibitors, tamsulosin, or any other component of <i>Jalyn</i>. WARNINGS AND PRECAUTIONS Intraoperative Floppy Iris Syndrome - Intraoperative Floppy Iris Syndrome has been observed during cataract surgery in some patients on or previously treated with alpha adrenergic antagonists. ADVERSE REACTIONS - Reproductive System and Breast Disorders: Testicular pain and testicular swelling Postmarketing Experience - Psychiatric Disorders: Depressed mood http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351843.htm
Ezogabine <i>Potiga</i> (GlaxoSmithKline)	Can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina. It is unknown if these changes are reversible. http://www.fda.gov/Drugs/DrugSafety/ucm349538.htm
Fidaxomicin <i>Difcid</i> (Optimer Pharms)	CONTRAINDICATIONS - Hypersensitivity WARNINGS AND PRECAUTIONS - Acute Hypersensitivity Reactions: Acute hypersensitivity reactions, including dyspnea, rash, pruritus, and angioedema of the mouth, throat, and face have been reported with fidaxomicin. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351536.htm

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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
Ibandronate <i>Boniva</i> (Roche)	<i>Boniva</i> (ibandronate) injection CONTRAINDICATIONS Cases of anaphylaxis, including: - Fatal events, have been reported. WARNINGS AND PRECAUTIONS Anaphylactic Reaction: - Cases of anaphylaxis, including fatal events, have been reported in patients treated with <i>Boniva</i> injection. - Osteonecrosis of the Jaw: Osteonecrosis of the jaw has been reported in patients treated with bisphosphonates. Musculoskeletal Pain: - Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking <i>Boniva</i> and other bisphosphonates. ADVERSE REACTIONS Postmarketing Experience – Hypersensitivity: - Asthma exacerbation - Anaphylactic reaction http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351740.htm
Tolvaptan <i>Samsca</i> (Otsuka)	Used should be limited to 30 days or less and avoided in patients with underlying liver disease. Prolonged use or use in patients with liver disease can increase the risk of liver problems, including life-threatening liver failure. http://www.fda.gov/Drugs/DrugSafety/ucm350062.htm
Valproate sodium & related compounds (Various)	Valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. There is evidence that these medications can cause decreased IQ scores in children whose mothers took them while pregnant. http://www.fda.gov/Drugs/DrugSafety/ucm350684.htm

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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
Zolpidem <i>Ambien</i> , <i>Ambien CR</i> , <i>Edluar</i> (Various)	Class labeling change: new dosing recommendations for all zolpidem problems. CONTRAINDICATIONS • <i>Ambien</i> is contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions include anaphylaxis and angioedema. WARNINGS AND PRECAUTIONS • <i>Ambien</i>, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (eg, benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. • Abnormal Thinking and Behavioral Changes: In controlled trials of <i>Ambien</i> 10 mg taken at bedtime, < 1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with <i>Ambien</i> 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo. • Use in Patients with Depression: In primarily depressed patients treated with sedative-hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. • Respiratory Depression: Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease, there was a reduction in the total arousal index. • Withdrawal Effects: There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence. USE IN SPECIFIC POPULATIONS Gender Difference in Pharmacokinetics: • Women clear zolpidem tartrate from the body at a lower rate than men. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351817.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm351833.htm

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