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): February 18, 2013 through March 15, 2013

Ado-trastuzumab emtansine – Kadcyla (Genentech)	
<i>Comparative agents:</i>	Trastuzumab
<i>Indication:</i>	Treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy
<i>Mechanism of action:</i>	HER2-targeted antibody and microtubule inhibitor conjugate
<i>Common adverse effects:</i>	Fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation
<i>Dosage form & strength:</i>	Injection; 100 mg/vial or 160 mg/vial
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf
Ospemifene – Osphena (Shionogi)	
<i>Comparative agents:</i>	Estrogen
<i>Indication:</i>	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
<i>Mechanism of action:</i>	Estrogen agonist/antagonist
<i>Common adverse effects:</i>	Hot flush, vaginal discharge, muscle spasms, genital discharge, hyperhidrosis
<i>Dosage form & strength:</i>	Tablet: 60 mg
<i>Product labeling:</i>	http://www.shionogi.com/pdf/PI/Osphena-PI.pdf

Table 2. New dosage forms and indications approved by the FDA: February 18, 2013 through March 15, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/ route of administration		
Aripiprazole	Abilify Maintena (Otsuka Pharm)	Extended-release injection for treatment of schizophrenia

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Table 2. New dosage forms and indications approved by the FDA: February 18, 2013 through March 15, 2013 (CONT.)

Generic name	Brand name (Company)	Indication and comments
Immune globulin intravenous (human)	<i>Privigen</i> (CSL Behring)	40 g vial
New indications		
Factor XIII concentrate (human)	<i>Corifact</i> (CSL Behring)	Perioperative management of surgical bleeding in adult and pediatric patients with congenital factor XIII deficiency
Everolimus	<i>Zortress</i> (Novartis)	Prophylaxis of allograft rejection in adult patients receiving a liver transplant
Regorafenib	<i>Stivarga</i> (Bayer Healthcare)	Treatment of patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and that no longer respond to other FDA-approved treatments for this disease

Table 3. Agents pending FDA approval: February 18, 2013 through March 15, 2013

Generic name	Brand name (Company)	Indication and comments
Complete response letter: more information required		
Hepatitis B vaccine	<i>Heplisav</i> (Dynavax)	Additional data on safety and manufacturing requested
Recommended for NON-approval by an FDA advisory panel		
Calcitonin salmon	(Various)	Committee voted that the data no longer support the marketing of calcitonin salmon as a treatment for osteoporosis in postmenopausal women.
Gabapentin	<i>Sefelsa</i> (Depomed)	Insufficient efficacy data to support approval for use in the treatment of menopausal symptoms
Paroxetine mesylate	(Hisamitsu Pharmaceuticals)	Insufficient efficacy data to support approval for use in the treatment of menopausal symptoms
Rivaroxaban	<i>Xarelto</i> (Janssen Pharmaceuticals)	More data required for acute coronary syndrome indication
Agents scheduled for review by an FDA advisory panel		
Tivozanib	(AVEO Oncology & Astellas Pharma)	Treatment of patients with advanced renal cell carcinoma

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

Generic name Brand name (Company)	Warning
Angiotensin converting enzyme inhibitors (Various)	Do not co-administer aliskiren with angiotensin-converting enzyme inhibitors with aliskiren in patients with diabetes. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342027.htm?source=govdelivery
Azithromycin (Various)	WARNINGS QT Prolongation <ul style="list-style-type: none"> • Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including: <ul style="list-style-type: none"> ◦ patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure, ◦ patients on drugs known to prolong the QT interval, ◦ patients with ongoing proarrhythmic conditions (eg, uncorrected hypokalemia). http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342027.htm?source=govdelivery
Boceprevir <i>Victrelis</i> (Merck Sharp Dohme)	WARNINGS AND PRECAUTIONS Pregnancy (Use with Ribavirin and Peginterferon Alfa) <ul style="list-style-type: none"> • One of these forms of contraception can be a combined oral contraceptive product containing at least 1 mg of norethindrone. Oral contraceptives containing lower doses of norethindrone and other forms of hormonal contraception have not been studied or are contraindicated. Routine monthly pregnancy tests must be performed during this time. Anemia (Use with Ribavirin and Peginterferon Alfa) <ul style="list-style-type: none"> • If ribavirin is permanently discontinued for management of anemia, then peginterferon alfa and <i>Victrelis</i> must also be discontinued • In clinical trials, the median time to onset of hemoglobin less than 10 g per dL from the initiation of therapy was similar among subjects. Neutropenia (Use with Ribavirin and Peginterferon Alfa) <ul style="list-style-type: none"> • If peginterferon alfa and ribavirin are permanently discontinued, then <i>Victrelis</i> must also be discontinued. Laboratory Tests <ul style="list-style-type: none"> • Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating <i>Victrelis</i>/peginterferon alfa/ribavirin combination therapy. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303600.htm
Clonidine hydrochloride <i>Kapvay</i> (Shionogi)	WARNINGS AND PRECAUTIONS Cardiac Conduction Abnormalities <ul style="list-style-type: none"> • The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There have been postmarketing reports of patients with conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring IV atropine, IV isoproterenol, and temporary cardiac pacing while taking clonidine. Up titrate <i>Kapvay</i> slowly and monitor vital signs frequently in patients with cardiac conduction abnormalities or patients concomitantly treated with other sympatholytic drugs. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342967.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
Darunavir <i>Prezista</i> (Janssen Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Pediatric Patients</p> <ul style="list-style-type: none"> Do not administer <i>Prezista</i>/ritonavir in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age. <p>ADVERSE REACTIONS</p> <p>Clinical Trials Experience: Pediatric Patients</p> <ul style="list-style-type: none"> <i>Prezista</i>/ritonavir has been studied in combination with other antiretroviral agents in 3 phase II trials in a small number of pediatric patients. <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> Antimalarials: artemether/lumefantrine – No change in darunavir exposures. Decrease in artemether and dihydroartemisinin exposures. Increase in lumefantrine exposures. The combination of <i>Prezista</i> and artemether/lumefantrine can be used without dose adjustments. However, the combination should be used with caution as increased lumefantrine exposure may increase the risk of QT prolongation. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm211904.htm</p>
Denosumab <i>Xgeva</i> (Amgen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypocalcemia</p> <ul style="list-style-type: none"> <i>Xgeva</i> can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct preexisting hypocalcemia prior to <i>Xgeva</i> treatment. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when <i>Xgeva</i> is administered with other drugs that can also lower calcium levels. Advise patients to contact a health care professional for symptoms of hypocalcemia. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm343116.htm</p>
Epirubicin hydrochloride <i>Ellence</i> for injection (Pfizer)	<p>CONTRAINDICATIONS</p> <p>Patients should not be treated with epirubicin hydrochloride injection if they have any of the following conditions:</p> <ul style="list-style-type: none"> Cardiomyopathy and/or heart failure, recent myocardial infarction, or severe arrhythmias. <p>WARNINGS AND PRECAUTIONS</p> <p>Pregnancy</p> <ul style="list-style-type: none"> Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods. <p>ADVERSE REACTIONS</p> <p>Overview of Acute and Delayed Toxicities</p> <ul style="list-style-type: none"> Other serious drug-related cardiovascular adverse events that occurred during clinical trials with epirubicin hydrochloride, administered in different indications, include ventricular tachycardia, AV block, bundle branch block, bradycardia, and thromboembolism. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm343125.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
Etravirine <i>Intence</i> (Janssen Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Severe Skin and Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme. Hypersensitivity reactions including drug rash with eosinophilia and systemic symptoms (DRESS) have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction. <p>ADVERSE REACTIONS</p> <p>Clinical Trial Experience: Adults</p> <ul style="list-style-type: none"> The incidence of rash was higher in women compared to men in the <i>Intence</i> arm in the phase 3 trials (rash $\geq$ grade 2 was reported in 15% women vs 9.5% men; discontinuations due to rash were reported in 5% women vs 1.9% men). <p>Clinical Trials Experience: Pediatric Subjects (6 years to less than 18 years of age)</p> <ul style="list-style-type: none"> Rash was reported more frequently in female subjects than in male subjects (rash $\geq$ grade 2 was reported in 20.3% females vs 5.4% males); discontinuations due to rash were reported in 4% of subjects (6.3% females vs 0% males). Rash ($\geq$ grade 2) occurred in 15% of pediatric subjects. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm239762.htm</p>
Everolimus <i>Zortress</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hepatic Artery Thrombosis</p> <ul style="list-style-type: none"> Mammalian target of rapamycin (mTOR) inhibitors are associated with an increase in hepatic artery thrombosis (HAT). Reported cases mostly have occurred within the first 30 days post transplant and most also lead to graft loss or death. Therefore, <i>Zortress</i> should not be administered earlier than 30 days after liver transplant. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303659.htm</p>
Exemestane <i>Aromasin</i> (Pharmacia & Upjohn)	<p>WARNINGS AND PRECAUTIONS</p> <p>Vitamin D Assessment</p> <ul style="list-style-type: none"> Routine assessment of 25-hydroxy vitamin D levels prior to the start of aromatase inhibitor treatment should be performed, due to the high prevalence of vitamin D deficiency in women with early breast cancer (EBC). Women with vitamin D deficiency should receive supplementation with vitamin D. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250607.htm</p>
Maraviroc <i>Selzentry</i> (ViiV Healthcare)	<p>WARNINGS AND PRECAUTIONS</p> <p>Severe Skin and Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Severe, potentially life-threatening skin and hypersensitivity reactions have been reported in patients taking <i>Selzentry</i>, in most cases concomitantly with other drugs associated with these reactions. These include cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS. The cases were characterized by features including rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. Discontinue <i>Selzentry</i> and other suspected agents immediately if signs or symptoms of severe skin or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, lip swelling, eosinophilia). Delay in stopping treatment with <i>Selzentry</i> or other suspect drugs after the onset of rash may result in a life-threatening reaction. Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Severe skin and hypersensitivity reactions <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm215506.htm</p>
Peginesatide <i>Omontys</i> (Affymax)	<p>All lots recalled because of severe hypersensitivity reactions, including fatalities.</p> <p>http://www.medpagetoday.com/HematologyOncology/Anemia/37509</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
Propafenone hydrochloride <i>Rythmol SR</i> (GlaxoSmithKline)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Known Brugada syndrome <p>WARNINGS AND PRECAUTIONS</p> <p>Unmasking Brugada syndrome</p> <ul style="list-style-type: none"> Brugada syndrome may be unmasked after exposure to <i>Rythmol SR</i>. Perform an ECG after initiation of <i>Rythmol SR</i> and discontinue the drug if changes are suggestive of Brugada syndrome. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm343128.htm</p>
Varenicline <i>Chantix</i> (Pfizer)	<p>WARNINGS AND PRECAUTIONS</p> <p>Neuropsychiatric Symptoms and Suicidality</p> <ul style="list-style-type: none"> Limited data are available from a single smoking cessation study in patients with stable schizophrenia or schizoaffective disorder. <p>ADVERSE REACTIONS</p> <p>Clinical Trials Experience</p> <ul style="list-style-type: none"> Include information on the safety and tolerability of <i>Chantix</i> in patients with schizophrenia and schizoaffective disorder. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm190335.htm</p>

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