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: July 13, 2015 through August 19, 2015

Adapalene benzoyl peroxide – Epiduo Forte Gel (Galderma)	
<i>Comparative agents:</i>	Individual ingredients
<i>Indication:</i>	Treatment of acne vulgaris
<i>Mechanism of action:</i>	Modulator of cellular differentiation, keratinization, and inflammatory processes and oxidizing agent with bactericidal and keratolytic effects
<i>Common adverse effects:</i>	Skin irritation, eczema, atopic dermatitis, and skin burning sensation
<i>Dosage form & strength:</i>	Gel; 0.3%/2.5%
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207917s000lbl.pdf
Alirocumab – Praluent (Sanofi/Regeneron)	
<i>Comparative agents:</i>	Evolocumab
<i>Indication:</i>	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
<i>Mechanism of action:</i>	PCSK9 inhibitor
<i>Common adverse effects:</i>	Nasopharyngitis, injection site reactions, and influenza
<i>Dosage form & strength:</i>	Pre-filled pen and syringe; 75 mg/mL and 150 mg/mL
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125559Orig1s000lbl.pdf
Daclatasvir – Daklinza (Bristol-Myers Squibb)	
<i>Comparative agents:</i>	Sofosbuvir
<i>Indication:</i>	Treatment of chronic hepatitis C genotype 3 infections with sofosbuvir
<i>Mechanism of action:</i>	NS5A inhibitor and NS5B polymerase inhibitor
<i>Common adverse effects:</i>	Headache and fatigue
<i>Dosage form & strength:</i>	Tablets; 30 mg and 60 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206843Orig1s000lbl.pdf

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Table 1. New drugs approved by the US Food and Drug Administration: July 13, 2015 through August 19, 2015 (CONT.)

Dichlorphenamide – Keveyis (Taro)	
<i>Comparative agents:</i>	Acetazolamide
<i>Indication:</i>	Treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants
<i>Mechanism of action:</i>	Oral carbonic anhydrase inhibitor
<i>Common adverse effects:</i>	Paresthesias, cognitive disorder, dysgeusia, and confusional state
<i>Dosage form & strength:</i>	Tablets; 40 mg
<i>Product labeling:</i>	http://www.keveyis.com/FINAL%20Approved%20Keveyis%20PI_%208.7.15.pdf
Ombitasvir/Paritaprevir/Ritonavir – Technivie (AbbVie)	
<i>Comparative agents:</i>	Ombitasvir/Paritaprevir/Ritonavir
<i>Indication:</i>	Indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis
<i>Mechanism of action:</i>	NS5A inhibitor, NS3/4A protease inhibitor, CYP3A inhibitor
<i>Common adverse effects:</i>	Asthenia, fatigue, nausea, and insomnia
<i>Dosage form & strength:</i>	Tablets; 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207931Orig1s000lbl.pdf
Sonidegib – Odomzo (Novartis)	
<i>Comparative agents:</i>	N/A
<i>Indication:</i>	Treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy
<i>Mechanism of action:</i>	Hedgehog pathway inhibitor
<i>Common adverse effects:</i>	Muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus
<i>Dosage form & strength:</i>	Capsule; 200 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205266s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: July 13, 2015 through August 18, 2015

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/route of administration		
Azelaic acid	Finacea Foam (Bayer HealthCare)	Topical treatment of inflammatory papules and pustules of mild to moderate rosacea http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207071s000lbl.pdf
New indications		
Abobotulinumtoxin A	Dysport (Ipsen Biopharmaceuticals)	Treatment of upper limb spasticity in adults
Carfilzomib	Kyprolis (Onyx Pharmaceuticals)	Used in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy

Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a

Generic name Brand name (Company)	Warning
AbobotulinumtoxinA <i>Dysport</i> (Ipsen Biopharm)	BOXED WARNING [edited] WARNING: DISTANT SPREAD OF TOXIN EFFECT Postmarketing reports indicate that the effects of <i>Dysport</i> and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose. http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm307392.htm
Atazanavir/cobicistat <i>Evotaz</i> (Bristol-Myers Squibb)	WARNINGS AND PRECAUTIONS Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions - Updated with information related to the co-administration of <i>Evotaz</i> and other medications metabolized by CPY3A DRUG INTERACTIONS Established and Other Potentially Significant Drug Interactions - Updated with information for patients initiating <i>Evotaz</i> while taking quetiapine and for patients initiating quetiapine while taking <i>Evotaz</i> http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458057.htm
Cabazitaxel <i>Jevtana</i> (sanofi-aventis)	CONTRAINDICATIONS - Severe hepatic impairment (total bilirubin >3 x upper limit of normal [ULN]) WARNINGS AND PRECAUTIONS - Bone marrow suppression (particularly neutropenia) and its clinical consequences (febrile neutropenia, neutropenic infections): Monitor blood counts frequently to determine if dosage modification or initiation of granulocyte-colony stimulating factor (G-CSF) is needed. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features. Use caution in patients with hemoglobin <10 g/dL. - <i>Jevtana</i> is contraindicated in patients with severe hepatic impairment (total bilirubin >3 x ULN). Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 x ULN or aspartate aminotransferase [AST] >1.5 x ULN) and moderate (total bilirubin >1.5 to ≤3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients. Administration of cabazitaxel to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392358.htm
Captopril <i>Capoten</i> (Par Pharmaceuticals)	CONTRAINDICATIONS - Do not co-administer aliskiren with <i>Capoten</i> in patients with diabetes. WARNINGS - Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (eg, temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258784.htm

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Ceftriaxone <i>Rocephin</i> (Hoffmann – La Roche)	CONTRAINDICATIONS Hypersensitivity • <i>Rocephin</i> is contraindicated in patients with known hypersensitivity to ceftriaxone, to any of its excipients, or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta-lactam antibacterial agents may be at greater risk of hypersensitivity to ceftriaxone. Neonates • Premature neonates: <i>Rocephin</i> is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age). Hyperbilirubinemic neonates: Hyperbilirubinemic neonates should not be treated with <i>Rocephin</i>. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients. Neonates Requiring Calcium Containing Intravenous (IV) Solutions • <i>Rocephin</i> is contraindicated in neonates (= 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium. • Cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving <i>Rocephin</i> and calcium-containing fluids. • In some of these cases, the same IV infusion line was used for both <i>Rocephin</i> and calcium-containing fluids, and in some a precipitate was observed in the IV infusion line. There have been no similar reports in patients other than neonates. Lidocaine • IV administration of ceftriaxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with ceftriaxone for intramuscular injection, exclude all contraindications to lidocaine. Refer to the prescribing information of lidocaine. WARNINGS Hypersensitivity Reactions • Before therapy with <i>Rocephin</i> is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, and other beta-lactam agents or other drugs. This product should be given cautiously to penicillin and other beta-lactam agent-sensitive patients. Antibacterial drugs should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures. • As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions (ie, anaphylaxis) have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. ADVERSE REACTIONS Postmarketing Experience • Gastrointestinal: Pancreatitis, stomatitis and glossitis. • Genitourinary: Oliguria, ureteric obstruction, post-renal acute renal failure. • Dermatologic: Exanthema, allergic dermatitis, urticaria, edema; acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome (SJS) or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	• Hematological changes: Isolated cases of agranulocytosis ($< 500/\text{mm}^3$) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more. • Nervous system disorders: Convulsion • Other, Adverse Reactions: Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm454350.htm
Ceftriaxone (various)	WARNINGS AND PRECAUTIONS Urolithiasis and postrenal acute renal failure • Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving ceftriaxone and may be detected as sonographic abnormalities. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of urolithiasis and ureteral obstruction and postrenal acute renal failure. The condition appears to be reversible upon discontinuation of ceftriaxone and institution of appropriate management. Ensure adequate hydration in patients receiving ceftriaxone. Discontinue ceftriaxone in patients who develop signs and symptoms suggestive of urolithiasis, oliguria, or renal failure and/or the sonographic findings described above. ADVERSE REACTIONS Postmarketing Experience • Genitourinary: ... ureteric obstruction, postrenal acute renal failure http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458059.htm
Ceritinib <i>Zykadia</i> (Novartis)	WARNINGS AND PRECAUTIONS Hepatotoxicity • ... Concurrent elevations in alanine aminotransferase (ALT) >3 times the ULN and total bilirubin >2 times the ULN, with normal alkaline phosphatase, occurred in $<1\%$ of patients in clinical studies... QT Interval Prolongation • QTc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmias (eg, torsade de pointes) or sudden death, occurred in patients treated with <i>Zykadia</i> in clinical trials... Hyperglycemia • ...Monitor fasting serum glucose prior to the start of <i>Zykadia</i> treatment and periodically thereafter as clinically indicated.... Pancreatitis • Pancreatitis, including one fatality, has been reported in $<1\%$ of patients receiving <i>Zykadia</i> in clinical trials. CTCAE grade 3-4 elevations of lipase and/or amylase occurred in 15% of patients receiving <i>Zykadia</i> in study 1. Monitor lipase and amylase prior to the start of <i>Zykadia</i> treatment and periodically thereafter as clinically indicated. Based on the severity of the laboratory abnormalities, withhold <i>Zykadia</i> with resumption at a reduced dose as described in Table 1. ADVERSE REACTIONS • Pancreatitis http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458065.htm

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Dapsone topical gel <i>Aczone</i> (Allergan)	WARNINGS AND PRECAUTIONS Methemoglobinemia - Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with <i>Aczone</i> gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of <i>Aczone</i> gel, 5% in those patients with congenital or idiopathic methemoglobinemia. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in, eg, buccal mucous membranes, lips, and nail beds. Advise patients to discontinue <i>Aczone</i> gel, 5% and seek immediate medical attention in the event of cyanosis. Dapsone can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents. Postmarketing Experience ...Methemoglobinemia has been identified during postmarketing use of <i>Aczone</i> gel, 5% Drug Interactions Concomitant Use with Drugs that Induce Methemoglobinemia - Concomitant use of <i>Aczone</i> with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk for developing methemoglobinemia. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458053.htm
Deferasirox <i>Exjade</i> (Novartis)	WARNINGS AND PRECAUTIONS Gastrointestinal (GI) Ulceration, Hemorrhage, and Perforation ... There have been reports of ulcers complicated with GI perforation (including fatal outcome) Severe Skin Reactions - If SJS or erythema multiforme is suspected... do not reintroduce <i>Exjade</i> therapy. - Skin rash: Reintroduction... after resolution of the rash. ADVERSE REACTIONS Postmarketing Experience - Renal and urinary disorders: Renal tubular necrosis... - Gastrointestinal disorders: ... gastrointestinal perforation http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm200643.htm
Denosumab <i>Xgeva</i> (Amgen)	WARNINGS AND PRECAUTIONS Hypocalcemia <i>Xgeva</i> can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to <i>Xgeva</i> treatment. Monitor calcium levels, throughout <i>Xgeva</i> therapy, especially in the first weeks of initiating therapy, 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. An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance <30 mL/min and/or on dialysis) and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	Osteonecrosis of the Jaw (ONJ) - Seventy-nine percent of patients with ONJ had a history of tooth extraction, poor oral hygiene, or use of a dental appliance as a predisposing factor. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections. - Perform an oral examination and appropriate preventive dentistry prior to the initiation of <i>Xgeva</i> and periodically during <i>Xgeva</i> therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with <i>Xgeva</i>. Consider temporary discontinuation of <i>Xgeva</i> therapy if an invasive dental procedure must be performed. There are no data available to suggest the optimal duration of treatment interruption. - Patients who are suspected of having or who develop ONJ while on <i>Xgeva</i> should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Clinical judgment of the treating physician should guide the management plan of each patient based on individual risk/benefit assessment. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303740.htm
Diazoxide <i>Proglycem</i> (Teva)	Risk of developing pulmonary hypertension in infants and newborns. All cases resolved after discontinuation of therapy. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm455659.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
Donepezil <i>Aricept</i> & <i>Aricept</i> ODT (Eisai)	POSTMARKETING EXPERIENCE The following adverse reaction terms were added: “rhabdomyolysis,” “QTc prolongation and torsade de pointes,” and “Stevens Johnson syndrome, and toxic epidermal necrolysis.” http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458056.htm
Doxazosin <i>Cardura XL</i> (Pfizer)	WARNINGS AND PRECAUTIONS - Priapism rarely (probably less frequently than once in every several thousand patients), alpha-1 antagonists, including doxazosin, have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition. ADVERSE REACTIONS ...gastrointestinal obstruction... http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208679.htm
Doxycycline <i>Doryx</i> (Warner Chilcott)	WARNINGS AND PRECAUTIONS Intracranial Hypertension Intracranial hypertension (IH; pseudotumor cerebri) has been associated with the use of tetracycline including <i>Doryx</i>. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on funduscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concomitant use of isotretinoin and <i>Doryx</i> because isotretinoin is also known to cause pseudotumor cerebri. Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm453969.htm

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Drospirenone/estradiol <i>Angeliq</i> (Bayer HealthCare)	WARNINGS AND PRECAUTIONS Hyperkalemia Consider monitoring serum potassium concentrations during the first month of dosing in high-risk patients who take strong CYP3A4 inhibitors long-term and concomitantly. Strong CYP3A4 inhibitors include azole antifungals (eg, ketoconazole, itraconazole, voriconazole), human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors (eg, indinavir, boceprevir), and clarithromycin. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm296119.htm
Drospirenone/ethinyl estradiol <i>Yasmin, Yaz</i> (Bayer HealthCare)	WARNINGS AND PRECAUTIONS Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly. Strong CYP3A4 inhibitors include azole antifungals (eg, ketoconazole, itraconazole, voriconazole), HIV/HCV protease inhibitors (eg, indinavir, boceprevir), and clarithromycin. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm453967.htm
Drospirenone/ethinyl estradiol/levomefolate calcium <i>Safyral, Beyaz</i> (Bayer HealthCare)	WARNINGS AND PRECAUTIONS Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly. Strong CYP3A4 inhibitors include azole antifungals (eg, ketoconazole, itraconazole, voriconazole), HIV/HCV protease inhibitors (eg, indinavir, boceprevir), and clarithromycin. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm453967.htm
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate <i>Stribild</i> (Gilead Sciences)	CONTRAINDICATIONS Updated with information related to the anticonvulsant medications carbamazepine, phenobarbital, and phenytoin. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm430199.htm
Etoposide phosphate <i>Etopophos</i> (Bristol Myers Squibb)	WARNINGS - New Pregnancy subsection entitled “Infertility” to provide information regarding contraception precautions and potential loss of fertility PRECAUTIONS Drug Interactions - Updated to include information on concomitant use of antiepileptic medications http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250461.htm
Filgrastim <i>Neupogen</i> (Amgen)	WARNINGS AND PRECAUTIONS Glomerulonephritis - Glomerulonephritis has occurred in patients receiving <i>Neupogen</i>. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of <i>Neupogen</i>. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of <i>Neupogen</i>. ADVERSE REACTION Postmarketing Experience ...glomerulonephritis... http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm219032.htm
Fingolimod <i>Gilenya</i> (Novartis)	WARNINGS AND PRECAUTIONS Infections Addition of information with respect to cryptococcal infections, including cases of cryptococcal meningitis http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm266123.htm

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Hydroxyurea <i>Droxia</i> (Bristol-Myers Squibb)	BOXED WARNING [edited] WARNING: MYELOSUPPRESSION AND MALIGNANCIES • Myelosuppression: <i>Droxia</i> may cause severe myelosuppression. Monitor blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary. • Malignancies: Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458082.htm
Insulin glargine <i>Lantus</i> (sanofi-aventis)	CONTRAINDICATIONS • During episodes of hypoglycemia ADVERSE REACTIONS • Hypokalemia http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm373727.htm
Mycophenolate <i>CellCept</i> (Roche)	WARNINGS Embryofetal Toxicity • The term “and nervous system” is added at the end of the subsection. Pure Red Cell Aplasia (PRC) • The words “should never” are replaced with the words “must not.” PRECAUTIONS Drug Interactions • Cyclosporine A interferes with mycophenolic acid (MPA) enterohepatic recirculation... changes in MPA exposure should be expected when switching patients from cyclosporine A to one of the immunosuppressants that do not interfere with MPA's enterohepatic cycle (eg, tacrolimus; belatacept)... Telmisartan • Concomitant administration of telmisartan and <i>CellCept</i> resulted in an approximately 30% decrease in MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity. PRECAUTIONS Pregnancy • Use of MMF during pregnancy... and nervous system. ADVERSE REACTIONS Postmarketing Experience • Congenital Disorders: ... including ear, facial, cardiac and nervous system malformations... • Hematologic and Lymphatic: ...and hypogammaglobulinemia... http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm310868.htm
Norgestimate/ethinyl estradiol <i>Ortho Tri-Cyclen Lo</i> (Janssen Pharms)	BOXED WARNING [edited] WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS • Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458080.htm

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Ombitasvir/paritaprevir/ ritonavir/dasabuvir <i>Viekira Pak</i> (AbbVie)	CONTRAINDICATIONS • ... Drugs that are moderate or strong inducers .... DRUG INTERACTIONS • Add quetiapine drug interaction information to Table 5 SPECIAL POPULATIONS Pregnancy • Update information regarding dasabuvir exposure in animals http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458365.htm
Oxybutynin <i>Gelnique, Oxytrol</i> (Actavis Labs)	WARNINGS Central Nervous System Effects • Addition of the terms “hallucinations” and “confusion” ADVERSE REACTIONS Postmarketing Experience • Addition of “hallucinations” and “confusion” http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm338239.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm241739.htm
Pembrolizumab <i>Keytruda</i> (Merck)	WARNINGS AND PRECAUTIONS Immune-Mediated Endocrinopathies Hypophysitis • Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one grade 2 and one grade 4 case (0.2% each), in patients receiving <i>Keytruda</i> in trial 1. The time to onset was 1.7 months for the patient with grade 4 hypophysitis and 1.3 months for the patient with grade 2 hypophysitis. Both patients were treated with high-dose (≥40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose. • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids for grade 2 or greater hypophysitis. Withhold <i>Keytruda</i> for moderate (grade 2) hypophysitis, withhold or discontinue <i>Keytruda</i> for severe (grade 3) hypophysitis, and permanently discontinue <i>Keytruda</i> for life-threatening (grade 4) hypophysitis. Thyroid Disorders • Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving <i>Keytruda</i> in trial 1. The median time to onset was 1.5 months (range 0.5-2.1). The median duration was 2.8 months (range 0.9-6.1). One of 2 patients with grade 2 and the 1 patient with grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (≥40 mg prednisone or equivalent per day) followed by a corticosteroid taper. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks to 19 months). No patient received corticosteroids or discontinued <i>Keytruda</i> for management of hypothyroidism. • Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. • Administer corticosteroids for grade 3 or greater hyperthyroidism, withhold <i>Keytruda</i> for severe (grade 3) hyperthyroidism, and permanently discontinue <i>Keytruda</i> for life-threatening (grade 4) hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

(continued)

Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
	Type 1 diabetes mellitus - Type 1 diabetes mellitus, including diabetic ketoacidosis, has occurred in patients receiving <i>Keytruda</i>. Monitor patients for hyperglycemia and other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold <i>Keytruda</i> in cases of severe hyperglycemia until metabolic control is achieved. Other Immune-Mediated Adverse Reactions - Across clinical studies with <i>Keytruda</i>, the following clinically significant, immune-mediated adverse reactions have occurred: severe dermatitis including bullous pemphigoid, myasthenic syndrome, optic neuritis, and rhabdomyolysis. - For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold <i>Keytruda</i> and administer corticosteroids. Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart <i>Keytruda</i> if the adverse reaction remains at grade 1 or less. Permanently discontinue <i>Keytruda</i> for any severe or grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction. Infusion-Related Reactions - Infusion-related reactions, including severe and life-threatening reactions, have occurred in patients receiving <i>Keytruda</i>. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritis, flushing, rash, hypotension, hypoxemia, and fever. For severe (grade 3) or life-threatening (grade 4) infusion-related reactions, stop infusion and permanently discontinue <i>Keytruda</i>. ADVERSE REACTIONS - Infusion-related reactions http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm454354.htm
Ruginamide <i>Banzel</i> (Eisai)	WARNINGS AND PRECAUTIONS Multi-organ Hypersensitivity/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) - DRESS, also known as multi-organ hypersensitivity, has been reported in patients taking antiepileptic drugs, including <i>Banzel</i>. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. Because this disorder is variable in its expression, other organ systems not noted here may be involved. - All cases of DRESS identified in clinical trials with <i>Banzel</i> occurred in pediatric patients less than 12 years of age, occurred within 4 weeks of treatment initiation, and resolved or improved with <i>Banzel</i> discontinuation. DRESS has also been reported in adult and pediatric patients taking <i>Banzel</i> in the postmarketing setting. - If DRESS is suspected, the patient should be evaluated immediately, <i>Banzel</i> should be discontinued, and alternative treatment should be started. ADVERSE REACTIONS - Postmarketing Experience: ...SJS and other serious skin rashes with mucosal involvement... http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm454353.htm

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Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic name Brand name (Company)	Warning
Synthetic conjugated estrogens, B <i>Enjuvia</i> (Teva)	BOXED WARNING [edited] WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA Estrogen-Alone Therapy Endometrial Cancer • There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. Cardiovascular Disorders and Probable Dementia • Estrogens-alone therapy should not be used for the prevention of cardiovascular disease or dementia. • The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50-79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo. • The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. • In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. • Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Estrogen Plus Progestin Therapy Cardiovascular Disorders and Probable Dementia • Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. • The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50-79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA). • The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. Breast Cancer • The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. • In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins. • Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

(continued)

Table 3. Significant labeling changes or “Dear Health Professional” letters related to safety^a

Generic name Brand name (Company)	Warning
	CONTRAINDICATIONS - Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders WARNINGS AND PRECAUTIONS - Hereditary angioedema: Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. ADVERSE REACTIONS Postmarketing Experience: The following adverse reactions have been identified during post-approval use of <i>Enjuvia</i>. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. - Gastrointestinal disorders: abdominal discomfort, abdominal distension, nausea; - Immune system disorders: anaphylactic reaction, hypersensitivity; - Musculoskeletal and connective tissue disorders: muscle spasms; - Nervous system disorders: headache, dizziness; - Psychiatric disorders: insomnia; - Reproductive system and breast disorders: breast pain, breast tenderness; - Skin and subcutaneous tissue disorders: alopecia, rash, urticarial; - Vascular disorders: deep vein thrombosis, thrombosis http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm454346.htm
Tofacitinib <i>Xeljanz</i> (Pfizer)	WARNINGS AND PRECAUTIONS - Viral reactivation: The risk of herpes zoster is increased in patients treated with <i>Xeljanz</i> and appears to be higher in patients treated with <i>Xeljanz</i> in Japan. USE IN SPECIFIC POPULATIONS - Use in diabetics: As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392730.htm
Topotecan <i>Hycamtin</i> (GlaxoSmithKline)	BOXED WARNING [edited] Bone Marrow Suppression <i>Hycamtin</i> can cause severe myelosuppression. Administer only to patients with baseline neutrophil counts of $\geq 1,500$ cells/mm³ and platelet counts $\geq 100,000$ cells/mm³. Monitor blood cell counts. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208464.htm
Zoledronic acid <i>Zometa</i> (Novartis)	WARNINGS AND PRECAUTIONS - The risk of ONJ may increase with duration of exposure to bisphosphonates. ADVERSE REACTIONS - Cases of SJS and toxic epidermal necrolysis have also been reported. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm244411.htm

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