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): October 18, 2013 through November 18, 2013

Eslicarbazepine acetate – Aptiom (Sunovion Pharmaceuticals)	
<i>Comparative agents:</i>	Oxcarbazepine
<i>Indication:</i>	Adjunctive treatment of partial-onset seizures
<i>Mechanism of action:</i>	Unknown; inhibition of voltage-gated sodium channels
<i>Common adverse effects:</i>	Dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor
<i>Dosage form & strength:</i>	Tablet; 200 mg, 400 mg, 600 mg, 800 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022416s000lbl.pdf
Hydrocodone bitartrate – Zohydro ER (Zogenix)	
<i>Comparative agents:</i>	Hydrocodone
<i>Indication:</i>	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
<i>Mechanism of action:</i>	Opioid agonist
<i>Common adverse effects:</i>	Constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, edema peripheral, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain, and tremor
<i>Dosage form & strength:</i>	Extended-release capsule: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880s000lbl.pdf
Ibrutinib – Imbruvica (Pharmacyclics)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of patients with mantle cell lymphoma who have received at least one prior therapy
<i>Mechanism of action:</i>	Kinase inhibitor
<i>Common adverse effects:</i>	Thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting, and decreased appetite
<i>Dosage form & strength:</i>	Capsule; 140 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf

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

Luliconazole – <i>Luzu</i> (MEDICIS)	
<i>Comparative agents:</i>	Clotrimazole, econazole, ketoconazole, miconazole, oxiconazole
<i>Indication:</i>	Topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms <i>Trichophyton rubrum</i> and <i>Epidermophyton floccosum</i> , in patients 18 years of age and older
<i>Mechanism of action:</i>	Exact mechanism of action; possibly inhibition of ergosterol synthesis by inhibiting the enzyme lanosterol demethylase
<i>Common adverse effects:</i>	Application site reactions
<i>Dosage form & strength:</i>	Cream; 1%
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204153s000lbl.pdf
Obinutuzumab – <i>Gazyva</i> (Genentech)	
<i>Comparative agents:</i>	None; first drug approval using the FDA's new breakthrough therapy designation
<i>Indication:</i>	Treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil
<i>Mechanism of action:</i>	CD20-directed cytolytic antibody
<i>Common adverse effects:</i>	Infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorder
<i>Dosage form & strength:</i>	Injection; each vial contains 1,000 mg/40 mL
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125486s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: October 18, 2013 – November 18, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/route of administration		
Insulin aspart [rDNA origin]	<i>Novolog</i> FlexTouch (Novo Nordisk)	Change in design of the insulin pen
Insulin detemir [rDNA origin]	<i>Levemir</i> FlexTouch (Novo Nordisk)	Change in design of the insulin pen
New indications		
Vigabatrin	<i>Sabril</i> (Lundbeck)	Add-on therapy for the treatment of refractory complex partial seizures in children 10 years of age and older who have inadequately responded to several other treatments and if the possible benefit outweighs the risk of vision loss

Table 3. Agents pending FDA approval: October 18, 2013 – November 18, 2013

Generic name	Brand name (Company)	Indication and comments
Recommended for approval by an FDA advisory panel		
Simeprevir	<i>Olysio</i> (Janssen)	Treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen (peginterferon alpha and ribavirin); efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis)
Sofosbuvir	(Gilead Sciences)	Treatment of chronic hepatitis C with ribavirin or pegylated interferon and ribavirin depending on the genotype.
Tasimelteon	<i>Hetlioz</i> (Vanda Pharmaceuticals)	Treatment of non-24-hour-disorder (non-24) in the totally blind patients

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

Generic name Brand name (Company)	Warning
Acetaminophen <i>Ofirmev</i> (Cadence Pharmaceuticals)	<p>BOXED WARNING</p> <p>WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY</p> <ul style="list-style-type: none"> Take care when prescribing, preparing, and administering <i>Ofirmev</i> injection to avoid dosing errors that could result in accidental overdose and death. In particular, be careful to ensure that: <ul style="list-style-type: none"> the dose in milligrams (mg) and milliliters (mL) is not confused; the dosing is based on weight for patients under 50 kg; infusion pumps are properly programmed; and the total daily dose of acetaminophen from all sources does not exceed maximum daily limits. <i>Ofirmev</i> contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits and often involve more than one acetaminophen-containing product. <p>WARNINGS AND PRECAUTIONS</p> <p>Hepatic Injury</p> <ul style="list-style-type: none"> The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products. <p>Serious Skin Reactions</p> <ul style="list-style-type: none"> Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity. <p>Risk of Medication Errors</p> <ul style="list-style-type: none"> Take care when prescribing, preparing, and administering <i>Ofirmev</i> (acetaminophen) injection in order to avoid dosing errors that could result in accidental overdose and death. In particular, be careful to ensure that: <ul style="list-style-type: none"> the dose in mg and mL is not confused; the dosing is based on weight for patients under 50 kg; infusion pumps are properly programmed; and the total daily dose of acetaminophen from all sources does not exceed maximum daily limits. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm373724.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
Alvimopan <i>Entereg</i> (Cubist Pharmaceuticals)	<p>BOXED WARNING</p> <p>WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE; FOR SHORT-TERM HOSPITAL USE ONLY</p> <ul style="list-style-type: none"> <i>Entereg</i> is available only through a restricted program for short-term use (15 doses) under a Risk Evaluation and Mitigation Strategy (REMS) called the Entereg Access Support and Education (E.A.S.E.) program. <p>WARNINGS AND PRECAUTIONS</p> <p>Gastrointestinal-Related Adverse Reactions in Opioid-Tolerant Patients</p> <ul style="list-style-type: none"> Patients recently exposed to opioids are expected to be more sensitive to the effects of μ-opioid receptor antagonists, such as <i>Entereg</i>. <p>Risk of Serious Adverse Reactions in Patients with Severe Hepatic Impairment</p> <ul style="list-style-type: none"> Patients with severe hepatic impairment may be at higher risk of serious adverse reactions (including dose-related serious adverse reactions) because up to 10-fold higher plasma levels of drug have been observed in such patients compared with patients with normal hepatic function. Therefore, the use in this patient population is not recommended. <p>Risk of Serious Adverse Reactions in Patients with Complete Gastrointestinal Obstruction</p> <ul style="list-style-type: none"> No studies have been conducted in patients with complete gastrointestinal obstruction or in patients who have surgery for correction of complete bowel obstruction. <i>Entereg</i> is not recommended for use in these patients. <p>Risk of Serious Adverse Reactions in Pancreatic and Gastric Anastomoses</p> <ul style="list-style-type: none"> <i>Entereg</i> has not been studied in patients having pancreatic or gastric anastomosis. Therefore, <i>Entereg</i> is not recommended for use in these patients. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194328.htm</p>
Butalbital, acetaminophen, caffeine and codeine phosphate <i>Fioricet with Codeine</i> (Watson Labs)	<p>WARNINGS</p> <p>Serious Skin Reactions</p> <ul style="list-style-type: none"> Rarely, acetaminophen may cause serious skin reactions such as AGEP, SJS, and TEN, which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm373726.htm</p>
Clarithromycin <i>Biaxin</i> products (AbbVie)	<p>WARNINGS</p> <p>Hepatotoxicity</p> <ul style="list-style-type: none"> Symptoms of hepatitis can include anorexia, jaundice, dark urine, pruritus, or tender abdomen. <p>Drug Interactions</p> <ul style="list-style-type: none"> Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme. <p>Benzodiazepines</p> <ul style="list-style-type: none"> Increased sedation and prolongation of sedation have been reported with concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam. <p>Oral Hypoglycemic Agents/Insulin</p> <ul style="list-style-type: none"> The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide, and rosiglitazone, inhibition of the CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

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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
	<p>Oral Anticoagulant</p> <ul style="list-style-type: none"> There is a risk of serious hemorrhage and significant elevations in the international normalized ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently. <p>HMG-CoA Reductase Inhibitors (statins)</p> <ul style="list-style-type: none"> Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4, and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Cases of rhabdomyolysis have been reported in patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment. Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with atorvastatin or pravastatin cannot be avoided, atorvastatin dose should not exceed 20 mg daily and pravastatin dose should not exceed 40 mg daily. Use of a statin that is not dependent on CYP3A metabolism (eg, fluvastatin) can be considered. It is recommended to prescribe the lowest registered dose if concomitant use cannot be avoided. <p>Combination therapy with other drugs</p> <ul style="list-style-type: none"> For information about warnings of other drugs indicated in combination with <i>Biaxin</i>, refer to the WARNINGS section of their package inserts. <p>PRECAUTIONS</p> <p>Efavirenz, Nevirapine, Rifampicin, Rifabutin, and Rifapentine</p> <ul style="list-style-type: none"> Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis <p>Etravirine</p> <ul style="list-style-type: none"> Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC. There have been spontaneous or published reports of CYP3A-based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, bromocriptine, vinblastine, phenobarbital, and St. John’s Wort. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258816.htm</p>
Clopidogrel bisulfate Plavix (sanofi-aventis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Allergic Cross-Reactivity</p> <ul style="list-style-type: none"> Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since allergic cross-reactivity among thienopyridines has been reported. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Respiratory, thoracic and mediastinal disorders: eosinophilic pneumonia Skin and subcutaneous tissue disorders: drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS) <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm225843.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
Crizotinib <i>Xalkori</i> (PF PRISM C.V.)	<p>WARNINGS AND PRECAUTIONS</p> <p>Bradycardia</p> <ul style="list-style-type: none"> Symptomatic bradycardia can occur in patients receiving <i>Xalkori</i>. Avoid using <i>Xalkori</i> in combination with other agents known to cause bradycardia (eg, beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of Grade 2 and 3 symptomatic bradycardia, hold <i>Xalkori</i>, re-evaluate the use of concomitant medications, and adjust the dose of <i>Xalkori</i>. <p>USE IN SPECIFIC POPULATIONS</p> <p>Renal Impairment</p> <ul style="list-style-type: none"> No starting dose adjustment is needed for patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min) and moderate (CLcr 30 to 59 mL/min) renal impairment, as steady-state trough concentrations in these 2 groups were similar to those in patients with normal renal function (CLcr = 90 mL/min) in Study B. Increased exposure to crizotinib occurred in patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis. Administer <i>Xalkori</i> at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment not requiring dialysis. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295722.htm</p>
Deferasirox <i>Exjade</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Severe Skin Reactions</p> <ul style="list-style-type: none"> Severe skin reactions, including SJS and erythema multiforme, have been reported during <i>Exjade</i> therapy. If SJS or erythema multiforme is suspected, discontinue <i>Exjade</i> and evaluate. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Skin and subcutaneous tissue disorders: SJS <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm255103.htm</p>
Desflurane <i>Suprane</i> (Baxter Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Induction of anesthesia in pediatric patients <p>WARNINGS AND PRECAUTIONS</p> <p>Respiratory Adverse Reactions in Pediatric Patients</p> <ul style="list-style-type: none"> <i>Suprane</i> (desflurane, USP) is not approved for maintenance of anesthesia in nonintubated children due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm, and secretions. <p>DRUG INTERACTIONS</p> <p>Neuromuscular Blocking Agents</p> <ul style="list-style-type: none"> Data changed/updated in Table 4 <p>USE IN SPECIFIC POPULATIONS</p> <p>Pediatric Use</p> <p>Respiratory Adverse Reactions in Pediatric Patients</p> <ul style="list-style-type: none"> <i>Suprane</i> (desflurane, USP) is indicated for maintenance of anesthesia in infants and children after induction of anesthesia with agents other than <i>Suprane</i> (desflurane, USP) and tracheal intubation. <i>Suprane</i> (desflurane, USP) is not approved for maintenance of anesthesia in nonintubated children due to an increased incidence of respiratory adverse reactions, including coughing (26%), laryngospasm (13%), and secretions (12%). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372692.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
Eletriptan <i>Relpax</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Hypersensitivity to <i>Relpax</i> (angioedema and anaphylaxis seen) <p>WARNINGS AND PRECAUTIONS</p> <p>Increase in Blood Pressure</p> <ul style="list-style-type: none"> Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT₁ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with <i>Relpax</i>. <i>Relpax</i> is contraindicated in patients with uncontrolled hypertension. <p>Anaphylactic/Anaphylactoid Reactions</p> <ul style="list-style-type: none"> There have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving <i>Relpax</i>. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. <i>Relpax</i> is contraindicated in patients with a history of hypersensitivity reaction to <i>Relpax</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm255038.htm</p>
Enoxaparin <i>Lovenox</i> (sanofi-aventis)	<p>BOX WARNING</p> <p>WARNING: SPINAL/EPIDURAL HEMATOMAS</p> <ul style="list-style-type: none"> Optimal timing between the administration of <i>Lovenox</i> and neuraxial procedures is not known. <p>WARNINGS AND PRECAUTIONS</p> <p>Increased Risk of Hemorrhage</p> <ul style="list-style-type: none"> To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Placement or removal of a catheter should be delayed for at least 12 hours after administration of lower doses (30 mg once or twice daily or 40 mg once daily) of <i>Lovenox</i>, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of <i>Lovenox</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm180210.htm</p>
Estradiol <i>Climara</i> (Bayer Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Known anaphylactic reaction or angioedema with <i>Climara/Pro</i> <p>WARNINGS AND PRECAUTIONS</p> <p>Hereditary Angioedema</p> <ul style="list-style-type: none"> Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374594.htm</p>
Estradiol <i>Menostar</i> (Bayer Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Known anaphylactic reaction or angioedema with Menostar Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders <p>WARNINGS AND PRECAUTIONS</p> <p>Hereditary Angioedema</p> <ul style="list-style-type: none"> Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374593.htm</p>

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

Generic name <i>Brand name</i> (Company)	Warning
Estradiol/levonorelrel <i>Climara Pro</i> (Bayer Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Known anaphylactic reaction or angioedema with <i>Climara Pro</i> <p>WARNINGS AND PRECAUTIONS</p> <p>Hereditary Angioedema</p> <ul style="list-style-type: none"> Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374594.htm</p>
Etonogestrel/ethinyl estradiol <i>NuvaRing</i> (Organon)	<p>WARNINGS AND PRECAUTIONS</p> <p>Thromboembolic Disorders and Other Vascular Problems</p> <ul style="list-style-type: none"> Stop <i>NuvaRing</i> use if an arterial thrombotic or venous thromboembolic event (VTE) occurs. Stop <i>NuvaRing</i> use if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. If feasible, stop <i>NuvaRing</i> at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism and during and following prolonged immobilization. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374592.htm</p>
Fondaparinux sodium <i>Arixtra</i> (GlaxoSmithKline)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> History of serious hypersensitivity reaction (eg, angioedema, anaphylactoid/anaphylactic reactions) to <i>Arixtra</i> <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Occurrence of serious allergic reactions (including angioedema and anaphylactoid/anaphylactic reactions) <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208639.htm</p>
Gadobutrol <i>Gadavist</i> (Bayer Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> <i>Gadavist</i> is contraindicated in patients with history of severe hypersensitivity reactions to <i>Gadavist</i>. <p>WARNINGS AND PRECAUTIONS</p> <p>Acute Kidney Injury</p> <ul style="list-style-type: none"> In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some gadolinium-based contrast agents (GBCAs). Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm373725.htm</p>
Gadopentetate dimeglumine <i>Magnevist</i> (Bayer Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> History of severe hypersensitivity reactions to <i>Magnevist</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm238544.htm</p>
Gadoxetate disodium <i>Eovist</i> (Bayer Healthcare)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> <i>Eovist</i> is contraindicated in patients with history of severe hypersensitivity reactions to <i>Eovist</i>. <p>WARNINGS AND PRECAUTIONS</p> <p>Acute Kidney Injury</p> <ul style="list-style-type: none"> In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs. The risk of acute kidney injury might be lower with <i>Eovist</i> due to its dual excretory pathways. Do not exceed the recommended dose. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm238203.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
Gemfibrozil <i>Lopid</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Combination therapy of gemfibrozil with simvastatin <p>WARNINGS</p> <ul style="list-style-type: none"> The concomitant administration of gemfibrozil with simvastatin is contraindicated. Concomitant therapy with <i>Lopid</i> and an HMG-CoA reductase inhibitor is associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis. <p>PRECAUTIONS</p> <p>Drug Interactions</p> <ul style="list-style-type: none"> HMG-CoA Reductase Inhibitors: The concomitant administration of <i>Lopid</i> with simvastatin is contraindicated. Colchicine: Myopathy, including rhabdomyolysis, has been reported with chronic administration of colchicine at therapeutic doses. Concomitant use of <i>Lopid</i> may potentiate the development of myopathy. Patients with renal dysfunction and elderly patients are at increased risk. Caution should be exercised when prescribing <i>Lopid</i> with colchicine, especially in elderly patients or patients with renal dysfunction. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm175927.htm</p>
Glyburide <i>Micronase</i> (Pharmacia & Upjohn)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Concomitant administration of bosentan. <p>PRECAUTIONS</p> <p>Drug Interactions</p> <ul style="list-style-type: none"> An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore concomitant administration of <i>Micronase</i> and bosentan is contraindicated. Colesevelam: Concomitant administration of colesevelam and glyburide resulted in reductions in glyburide AUC and C_{max} of 32% and 47%, respectively. The reductions in glyburide AUC and C_{max} were 20% and 15%, respectively, when administered 1 hour before and not significantly changed (-7% and 4%, respectively) when administered 4 hours before colesevelam. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm181158.htm</p>
Glyburide/metformin <i>Glucovance</i> (Bristol-Myers Squibb)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Concomitant administration of bosentan. <p>PRECAUTIONS</p> <p>Drug Interactions</p> <p>Glyburide</p> <ul style="list-style-type: none"> An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore concomitant administration of <i>Glucovance</i> and bosentan is contraindicated. Colesevelam: Concomitant administration of colesevelam and glyburide resulted in reductions in glyburide AUC and C_{max} of 32% and 47%, respectively. The reductions in glyburide AUC and C_{max} were 20% and 15%, respectively, when administered 1 hour before and not significantly changed (-7% and 4%, respectively) when administered 4 hours before colesevelam. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194334.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
Glyburide, micronized <i>Glynase</i> (Pharmacia & Upjohn)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Concomitant administration of bosentan. <p>PRECAUTIONS</p> <p>Drug Interactions</p> <ul style="list-style-type: none"> An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore concomitant administration of <i>Glynase</i> PresTab and bosentan is contraindicated. Colesevelam: Concomitant administration of colesevelam and glyburide resulted in reductions in glyburide AUC and C_{max} of 32% and 47%, respectively. The reductions in glyburide AUC and C_{max} were 20% and 15%, respectively, when administered 1 hour before and not significantly changed (-7% and 4%, respectively) when administered 4 hours before colesevelam. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm181153.htm</p>
Imatinib mesylate <i>Gleevec</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Embryo-fetal Toxicity</p> <ul style="list-style-type: none"> <i>Gleevec</i> can cause fetal harm when administered to a pregnant woman. Sexually active female patients of reproductive potential taking <i>Gleevec</i> should use highly effective contraception. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. <p>USE IN SPECIFIC POPULATIONS</p> <p>Pregnancy</p> <p>Risk Summary</p> <ul style="list-style-type: none"> <i>Gleevec</i> can cause fetal harm when administered to a pregnant woman. There have been postmarket reports of spontaneous abortions and infant congenital anomalies from women who have taken <i>Gleevec</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm255333.htm</p>
Insulin glargine [rDNA origin] <i>Lantus</i> (sanofi-aventis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Fluid retention and heart failure with concomitant use of peroxisome proliferator-activated receptor (PPAR)-gamma agonists</p> <ul style="list-style-type: none"> Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including <i>Lantus</i>, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm373727.htm</p>
Insulin glulisine <i>Apidra</i> (sanofi-aventis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Subcutaneous Insulin Infusion Pumps</p> <ul style="list-style-type: none"> When used in an external insulin pump for subcutaneous infusion, <i>Apidra</i> should not be diluted or mixed with any other insulin. <i>Apidra</i> in the reservoir must be changed at least every 48 hours. <i>Apidra</i> should not be exposed to temperatures greater than 98.6°F (37°C). Malfunction of the insulin pump or infusion set or handling errors or insulin degradation can rapidly lead to hyperglycemia, ketosis, and diabetic ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis or diabetic ketoacidosis is necessary. Interim subcutaneous injections with <i>Apidra</i> may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm371308.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
Lacosamide <i>Vimpat</i> (UCB)	<p>WARNINGS AND PRECAUTIONS</p> <p>Cardiac Rhythm and Conduction Abnormalities</p> <p>PR interval prolongation</p> <ul style="list-style-type: none"> Dose-dependent prolongations in PR interval with <i>Vimpat</i> have been observed in clinical studies in patients and in healthy volunteers. In clinical trials in patients with partial-onset epilepsy, asymptomatic first-degree atrioventricular (AV) block was observed as an adverse reaction in 0.4% (4/944) of patients randomized to receive <i>Vimpat</i> and 0% (0/364) of patients randomized to receive placebo. In clinical trials patients with diabetic neuropathy, asymptomatic first-degree AV block was observed as an adverse reaction in 0.5% (5/1023) of patients receiving <i>Vimpat</i> and 0% of patients receiving placebo. In the uncontrolled extension phases of pain studies, 2 subjects[sponsor to fill in denominator of trial patients] experienced AV block type 2. Neither of these subjects had 2nd degree block at baseline although both had either PR prolongation or 1st degree AV block at baseline. In one of these cases, the block was found as result of monitoring performed after an episode of syncope. When <i>Vimpat</i> is given with other drugs that prolong the PR interval, further prolongation is possible. <i>Vimpat</i> should be used with caution in patients with known conduction problems (eg, marked 1st-degree AVB, 2nd-degree or higher AVB and sick sinus syndrome without pacemaker, with sodium channelopathies (eg, Brugada Syndrome) on concomitant medications that prolong PR interval, or with severe cardiac disease such as myocardial ischemia or heart failure. In such patients, obtaining an ECG before beginning <i>Vimpat</i>, and after <i>Vimpat</i> is titrated to steady state, is recommended. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience:</p> <ul style="list-style-type: none"> The following adverse events have been reported during post-approval use of <i>Vimpat</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. Due to the need to balance the benefit of adding potentially serious medical events to the label and the risk that doing so will discourage future reporting of such events, health care providers and consumers are encouraged to continue reporting such events regardless of whether the event is already in this section. Cardiac disorders: 3rd degree AVB in epileptic patients <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> Patients with renal or hepatic impairment that are on strong inhibitors of CYP3A4 and CYP2C9 may have significant increase in exposure to <i>Vimpat</i>. Dose reduction may be necessary in these patients. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342620.htm</p>
Leuprolide acetate; Leuprolide acetate/norethindrone acetate <i>Lupron Depot & Lupaneta</i> pack (Abbott Laboratories)	<p>WARNINGS AND PRECAUTIONS</p> <p>Convulsions</p> <ul style="list-style-type: none"> There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374019.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
Linagliptin/metformin <i>Jentadueto</i> (Boehringer Ingelheim)	<p>WARNINGS AND PRECAUTIONS</p> <p>Pancreatitis</p> <ul style="list-style-type: none"> There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. <p>Use with Medications Known to Cause Hypoglycemia</p> <p>Linagliptin</p> <ul style="list-style-type: none"> Insulin secretagogues and insulin are known to cause hypoglycemia. The use of linagliptin in combination with an insulin secretagogue (eg, sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial, especially in patients with severe renal impairment. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with <i>Jentadueto</i>. <p>Note: labeling changes align the <i>Jentadueto</i> label with the updated information in the current <i>Tradjenta</i> label.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360497.htm</p>
Milnacipran <i>Savella</i> (Cypress Bioscience)	<p>CONTRAINDICATIONS</p> <p>Monoamine Oxidase Inhibitors (MAOIs)</p> <ul style="list-style-type: none"> The use of MAOIs intended to treat psychiatric disorders with <i>Savella</i> or within 5 days of stopping treatment with <i>Savella</i> is contraindicated because of an increased risk of serotonin syndrome. The use of <i>Savella</i> within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated. Starting <i>Savella</i> in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome. <p>WARNINGS AND PRECAUTIONS</p> <p>Serotonin Syndrome</p> <ul style="list-style-type: none"> The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including <i>Savella</i> alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort) and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). <p>Elevated Blood Pressure</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm203615.htm</p>
Mycophenolate mofetil <i>CellCept</i> (Roche)	<p>WARNINGS</p> <p>Infections</p> <p>Serious Infections</p> <ul style="list-style-type: none"> Patients receiving immunosuppressants, including <i>CellCept</i>, are at increased risk of developing bacterial, fungal, protozoal, and new or reactivated viral infections, including opportunistic infections. These infections may lead to serious, including fatal outcomes. Because of the danger of oversuppression of the immune system that can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution. <p>Latent Viral Infections</p> <p>New or Reactivated Viral Infections</p> <ul style="list-style-type: none"> Polyomavirus associated nephropathy (PVAN), JC virus associated progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) infections, reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including <i>CellCept</i>. Reduction in immunosuppression should be considered for patients who develop evidence of new or reactivated viral infections. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

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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
	<ul style="list-style-type: none"> • PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN. • PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. • The risk of CMV viremia and CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receives a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. • Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm310868.htm</p>
Mycophenolic acid <i>Myfortic</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Serious Infections</p> <ul style="list-style-type: none"> • Patients receiving immunosuppressants, including <i>Myfortic</i>, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, and new or reactivated viral infections including opportunistic infections. These infections may lead to serious, including fatal outcomes. Because of the danger of oversuppression of the immune system that can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution. <p>New or Reactivated Viral Infections</p> <ul style="list-style-type: none"> • PVAN, JC virus associated PML, CMV infections, reactivation of HBV or HCV have been reported in patients treated with immunosuppressants, including the mycophenolic acid (MPA) derivatives <i>Myfortic</i> and MMF. Reduction in immunosuppression should be considered for patients who develop evidence of new or reactivated viral infections. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft. • The risk of CMV viremia and CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receives a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. • Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm190429.htm</p>
Naltrexone <i>Revia</i> (TEVA)	<p>BOXED WARNING</p> <p><i>Removed.</i></p> <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Patients currently dependent on opioids including those currently maintained on opiate agonists (eg, methadone) or partial agonists (eg, buprenorphine). <p>WARNINGS</p> <p>Vulnerability to Opioid Overdose</p> <ul style="list-style-type: none"> • After opioid detoxification, patients are likely to have reduced tolerance to opioids. As the blockade of exogenous opioids provided by <i>Revia</i> wanes and eventually dissipates completely, patients who have been treated with <i>Revia</i> may respond to lower doses of opioids than previously used, just as they would shortly after completing detoxification. This could result in potentially life-threatening opioid

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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
	<p>intoxication (respiratory compromise or arrest, circulatory collapse, etc) if the patient uses previously tolerated doses of opioids. Cases of opioid overdose with fatal outcomes have been reported in patients after discontinuing treatment.</p> <ul style="list-style-type: none"> • Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after <i>Revia</i> treatment is discontinued. 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. • There is also the possibility that a patient who is treated with <i>Revia</i> could overcome the opioid blockade effect of <i>Revia</i>. Although <i>Revia</i> is a potent antagonist, the blockade produced by <i>Revia</i> is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade <p>Precipitated Opioid Withdrawal</p> <ul style="list-style-type: none"> • 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. Symptoms of withdrawal have usually appeared within 5 minutes of ingestion of <i>Revia</i> and have lasted for up to 48 hours. Mental status changes including confusion, somnolence, and visual hallucinations have occurred. <p>Hepatotoxicity</p> <ul style="list-style-type: none"> • Cases of hepatitis and clinically significant liver dysfunction were observed in association with <i>Revia</i> exposure during the clinical development program and in the postmarketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and postmarketing period. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease and hepatitis B and/or C infection. <p>Depression and Suicidality</p> <ul style="list-style-type: none"> • Depression, suicide, attempted suicide, and suicidal ideation have been reported in the postmarketing experience with <i>Revia</i> (naltrexone hydrochloride) used in the treatment of opioid dependence. No causal relationship has been demonstrated. In the literature, endogenous opioids have been theorized to contribute to a variety of conditions. • Alcohol- and opioid-dependent patients, including those taking <i>Revia</i>, should be monitored for the development of depression or suicidal thinking. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374896.htm</p>
Naratriptan <i>Amerge</i> (GlaxoSmithKline)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Hypersensitivity to <i>Amerge</i> (angioedema and anaphylaxis seen). <p>WARNINGS AND PRECAUTIONS</p> <p>Increase in Blood Pressure</p> <ul style="list-style-type: none"> • Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT₁ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with <i>Amerge</i>. <i>Amerge</i> is contraindicated in patients with uncontrolled hypertension.

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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
	<p>Anaphylactic/Anaphylactoid Reactions</p> <ul style="list-style-type: none"> There have been reports of anaphylaxis and anaphylactoid and hypersensitivity reactions, including angioedema, in patients receiving <i>Amerge</i>. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. <i>Amerge</i> is contraindicated in patients with a history of hypersensitivity reaction to <i>Amerge</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299303.htm</p>
Nilotinib <i>Tasigna</i> (Novartis)	<p>BOXED WARNING</p> <ul style="list-style-type: none"> Avoid food 2 hours before and 1 hour after taking the dose <p>WARNINGS AND PRECAUTIONS</p> <p>QT Prolongation</p> <ul style="list-style-type: none"> Before initiating <i>Tasigna</i> and periodically, test electrolyte, calcium, and magnesium blood levels. <p>Sudden Deaths</p> <ul style="list-style-type: none"> Sudden deaths have been reported in 0.3% of patients with chronic myelogenous leukemia (CML) treated with nilotinib in clinical studies of 5,661 patients. <p>Elevated Serum Lipase</p> <ul style="list-style-type: none"> <i>Tasigna</i> can cause increases in serum lipase. Patients with a previous history of pancreatitis maybe at greater risk. If lipase elevations...[sic] <p>Hepatotoxicity</p> <ul style="list-style-type: none"> <i>Tasigna</i> may result in hepatotoxicity as measured by elevations in bilirubin, AST/ALT, and alkaline phosphatase. Monitor hepatic function tests monthly or as clinically indicated. <p>Drug Interactions</p> <ul style="list-style-type: none"> Avoid administration of <i>Tasigna</i> with agents that are strong CYP3A4 inhibitors or anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other drugs that may prolong QT interval (including, but not limited to chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin, and pimozide) since nilotinib exposure will be increased. Should treatment with any of these agents be required, interrupt therapy with <i>Tasigna</i>. <p>Food Effects</p> <ul style="list-style-type: none"> The bioavailability of nilotinib is increased with food, thus <i>Tasigna</i> must not be taken with food. No food should be consumed for at least 2 hours before and for at least 1 hour after the dose is taken. Also avoid grapefruit products and other foods that are known to inhibit CYP3A4. <p>Hepatic Impairment</p> <ul style="list-style-type: none"> Nilotinib exposure is increased in patients with impaired hepatic function. Use a lower starting dose for patients with mild to severe hepatic impairment (at baseline) and monitor the QT interval frequently. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm182234.htm</p>
Ondansetron <i>Zuplenz</i> (Vestiq Pharms)	<p>WARNINGS AND PRECAUTIONS</p> <p>Electrocardiographic Changes</p> <ul style="list-style-type: none"> ECG changes including QT interval prolongation have been seen in patients receiving ondansetron. In addition, postmarketing cases of torsade de pointes have been reported in patients using ondansetron. Avoid <i>Zuplenz</i> in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities (eg, hypokalemia or hypomagnesemia), congestive heart failure, or bradyarrhythmias or in patients taking other medicinal products that lead to QT prolongation. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374020.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
Oral contraceptives, combination progestin/estrogen (birth control pills)—class labeling	<p>BOXED WARNING</p> <p>WARNINGS: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING</p> <ul style="list-style-type: none"> Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives should not be used by women who are over 35 years of age and smoke. <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Persistent blood pressure values of greater than 160 mm Hg systolic or greater than 100 mm Hg diastolic Addition of thrombophilic conditions as contraindications <p>WARNINGS</p> <p>Elevated Blood Pressure</p> <ul style="list-style-type: none"> Women with a history of hypertension or hypertension-related diseases, or renal disease⁷⁰ [sic] should be encouraged to use another method of contraception. If these women elect to use oral contraceptives, they should be monitored closely and if a clinically significant persistent elevation of blood pressure (BP) occurs (greater than 160 mm Hg systolic or greater than 100 mm Hg diastolic) and cannot be adequately controlled, oral contraceptives should be discontinued. In general, women who develop hypertension during hormonal contraceptive therapy should be switched to a non-hormonal contraceptive. If other contraceptive...[sic] <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374940.htm</p>
Piperacillin/tazobactam <i>Zosyn</i> (Wyeth)	<p>WARNINGS AND PRECAUTIONS</p> <p>Serious Skin Reactions</p> <ul style="list-style-type: none"> Serious skin reactions, such as SJS and TEN, have been reported in patients receiving <i>Zosyn</i>. If patients develop a skin rash they should be monitored closely and <i>Zosyn</i> discontinued if lesions progress. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Skin and Appendages—SJS, TEN <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm371312.htm</p>
Pitavastatin <i>Livalo</i> (Kowa)	<p>WARNINGS AND PRECAUTIONS</p> <ul style="list-style-type: none"> Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors coadministered with colchicine, and caution should be exercised when prescribing <i>Livalo</i> with colchicine <p>DRUG INTERACTIONS</p> <p>Colchicine</p> <ul style="list-style-type: none"> Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors coadministered with colchicine, and caution should be exercised when prescribing <i>Livalo</i> with colchicine. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm296184.htm</p>
Ponatinib <i>Iclusig</i> (Ariad Pharmaceuticals)	<p>Suspended marketing and sales because of the risk of life-threatening blood clots and severe narrowing of blood vessels. FDA will continue to evaluate the drug to further understand its risks and potential patient populations in which the benefits of the drug may outweigh the risks. Patients currently receiving ponatinib should discuss the risks and benefits of continuing treatment with the drug with their prescriber.</p> <p>http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm373072.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery</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
Quinapril <i>Accupril, Accuretic</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Do not co-administer aliskiren with <i>Accupril</i> in patients with diabetes or in patients with renal impairment (GFR < 60 mL/min/1.73 m²) <p>WARNINGS</p> <p>Anaphylactoid and Possibly Related Reactions</p> <ul style="list-style-type: none"> Patients taking concomitant mTOR inhibitor (eg, temsirolimus) therapy may be at increased risk for angioedema. <p>PRECAUTIONS</p> <p>Drug Interactions</p> <ul style="list-style-type: none"> Agents that inhibit mTOR: Patients taking concomitant mTOR inhibitor (eg, temsirolimus) therapy may be at increased risk for angioedema. <p>Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAS)</p> <p>The following text was added/deleted:</p> <ul style="list-style-type: none"> Do not co-administer aliskiren with <i>Accupril</i> in patients with diabetes with renal impairment (GFR <60 mL/min/1.73 m²). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm279812.htm</p>
Ramipril <i>Altace</i> (King Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Do not co-administer aliskiren with <i>Altace</i> in patients with diabetes or in patients with renal impairment (GFR < 60 mL/min/1.73 m²) <p>WARNINGS AND PRECAUTIONS</p> <p>Anaphylactoid and Possibly Related Reactions</p> <ul style="list-style-type: none"> Patients taking concomitant mTOR inhibitor (eg, temsirolimus) therapy may be at increased risk for angioedema. <p>Dual Blockade of the Renin-Angiotensin-Aldosterone System</p> <ul style="list-style-type: none"> Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on <i>Altace</i> and other agents that affect the RAS. <p>Aliskiren</p> <ul style="list-style-type: none"> Do not co-administer aliskiren with <i>Altace</i> in patients with diabetes or in patients with renal impairment (GFR <60 mL/min/1.73 m²). <p>DRUG INTERACTIONS</p> <p>Aliskiren</p> <ul style="list-style-type: none"> Do not co-administer aliskiren with <i>Altace</i> in patients with diabetes or in patients with renal impairment (GFR <60 mL/min/1.73 m²). <p>mTOR Inhibitors</p> <ul style="list-style-type: none"> Patients taking concomitant mTOR inhibitor (eg, temsirolimus) therapy may be at increased risk for angioedema. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm233254.htm</p>
Rivastigmine tartrate <i>Exelon</i> (Novartis)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Previous history of application site reaction with rivastigmine transdermal patch suggestive of allergic contact dermatitis, in the absence of negative allergy testing Isolated cases of generalized skin reactions have been described in postmarketing experience. <p>WARNINGS AND PRECAUTIONS</p> <p>Hypersensitivity Reactions of the Skin</p> <ul style="list-style-type: none"> There have been isolated postmarketing reports of patients experiencing disseminated hypersensitivity reactions of the skin when administered rivastigmine irrespective of the route of administration (oral or transdermal). Treatment should be discontinued if disseminated hypersensitivity reaction of the skin occurs. Patients and caregivers should be instructed accordingly.

(continued)

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

Generic name Brand name (Company)	Warning
	<ul style="list-style-type: none"> In patients who develop application site reactions suggestive of allergic contact dermatitis to <i>Exelon</i> patch and who still require rivastigmine, treatment should be switched to oral rivastigmine only after negative allergy testing and under close medical supervision. It is possible that some patients sensitized to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm373593.htm</p>
Simvastatin containing products <i>Juvisync</i> , <i>Vytorin</i> , <i>Zocor</i> (Merck Sharp Dohme)	<p>WARNINGS AND PRECAUTIONS</p> <p>Myopathy/Rhabdomyolysis</p> <ul style="list-style-type: none"> The benefits of the combined use of <i>Vytorin/Zocor/Juvisync</i> with the following drugs should be carefully weighed against the potential risks of combinations: other lipid-lowering drugs (other fibrates, =1 g/day of niacin; or, for patients with HoFH, lomitapide), amiodarone, dronedarone, verapamil, diltiazem, amlodipine, or ranolazine <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374242.htm</p>
Sitagliptin/metformin <i>Janumet</i> (Merck)	<p>CONTRAINDICATIONS</p> <p><i>Janumet</i> (sitagliptin/metformin HCl) is contraindicated in patients with:</p> <ul style="list-style-type: none"> Renal impairment (eg, serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. Hypersensitivity to metformin hydrochloride. Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin. <p>WARNINGS AND PRECAUTIONS</p> <p>Lactic Acidosis</p> <p>Metformin hydrochloride</p> <ul style="list-style-type: none"> The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. <p>Assessment of Renal Function</p> <ul style="list-style-type: none"> Therefore, <i>Janumet</i> is contraindicated in patients with renal impairment. <p>Sitagliptin</p> <ul style="list-style-type: none"> There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with <i>Janumet</i> and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and <i>Janumet</i> discontinued if evidence of renal impairment is present. <p>DRUG INTERACTIONS</p> <p>Carbonic Anhydrase Inhibitors</p> <ul style="list-style-type: none"> Topiramate or other carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with <i>Janumet</i>, as the risk of lactic acidosis may increase.

(continued)

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

Generic name Brand name (Company)	Warning
	<p>USE IN SPECIFIC POPULATIONS</p> <p>Renal Impairment</p> <ul style="list-style-type: none"> • “insufficiency” changed to “impairment” <p>Hepatic Impairment</p> <ul style="list-style-type: none"> • “insufficiency” changed to “impairment” <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372690.htm</p>
Tacrolimus <i>Prograf</i> (Astellas)	<p>WARNINGS AND PRECAUTIONS</p> <p>Use with CYP3A4 Inhibitors and Inducers</p> <ul style="list-style-type: none"> • When coadministering <i>Prograf</i> with strong CYP3A4-inhibitors (eg, telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (eg, rifampin, rifabutin), adjustments in the dosing regimen of <i>Prograf</i> and subsequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions are recommended. <p>QT Prolongation</p> <ul style="list-style-type: none"> • <i>Prograf</i> may prolong the QT/QTc interval and may cause torsade de pointes. Avoid <i>Prograf</i> in patients with congenital long QT prolongation syndrome. In patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia, consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment. • When coadministering <i>Prograf</i> with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in <i>Prograf</i> dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of <i>Prograf</i> with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation. <p>Gastrointestinal Perforation</p> <ul style="list-style-type: none"> • Gastrointestinal perforation has been reported in patients treated with tacrolimus; all reported cases were considered to be a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation may be serious or life threatening, appropriate medical/surgical management should be instituted promptly. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> • Gastrointestinal perforation <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> • Dose adjustments may be needed along with frequent monitoring of tacrolimus whole blood trough concentrations when <i>Prograf</i> is administered with CYP3A inhibitors or inducers. In addition, patients should be monitored for adverse reactions including changes in renal function and QT prolongation. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295069.htm</p>
Telaprevir <i>Incivek</i> (Vertex Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Table 3: Drugs that are Contraindicated with <i>Incivek</i> • Anticonvulsants: Carbamazepine, phenobarbital, phenytoin <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> • Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction • Analgesics: alfentanil, fentanyl • Drug interactions with carbamazepine and phenytoin were added. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm352014.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
Tenofovir-containing products	<p>WARNINGS AND PRECAUTIONS</p> <p>New Onset or Worsening Renal Impairment</p> <ul style="list-style-type: none"> It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with <i>Viread/Stribild/Truvada/Complera/Atripla</i>. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving <i>Hespera</i>, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of <i>Viread/Stribild/Truvada/Complera/Atripla</i>, and periodically during <i>Viread/Stribild/Truvada/Complera/Atripla</i> therapy. <i>Viread/Stribild/Truvada/Complera/Atripla</i> should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]). <p>Bone Effects of Tenofovir DF</p> <p>Bone Mineral Density:</p> <ul style="list-style-type: none"> In clinical trials in HIV-1 infected adults, <i>Viread/Stribild/Truvada/Complera/Atripla</i> was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving <i>Viread/Stribild/Truvada/Complera/Atripla</i>. Clinical trials evaluating <i>Viread</i> in pediatric and adolescent subjects were conducted. <p>Mineralization Defects:</p> <ul style="list-style-type: none"> Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and that may contribute to fractures, have been reported in association with the use of <i>Viread/Stribild/Truvada/Complera/Atripla</i>. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF. <p>ADVERSE REACTIONS</p> <p>Adverse Reactions from Clinical Trials Experience</p> <p>Changes in Bone Mineral Density:</p> <ul style="list-style-type: none"> Clinical trials in HIV-1–infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at week 48 was less in the <i>Viread/Stribild/Truvada/Complera/Atripla</i> compared to the placebo treatment group. <p>DRUG INTERACTIONS</p> <p>HIV-1 Protease Inhibitors</p> <ul style="list-style-type: none"> <i>Viread/Stribild/Truvada/Complera/Atripla</i> decreases the AUC and C_{min} of atazanavir. When coadministered with <i>Viread/Stribild/Truvada</i>, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. <i>Viread/Stribild/Truvada</i> should not be coadministered with atazanavir without ritonavir. Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving <i>Viread/Stribild/Truvada</i> concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for <i>Viread/Stribild/Truvada</i>–associated adverse reactions. <i>Viread/Stribild/Truvada</i> should be discontinued in patients who develop <i>Viread/Stribild/Truvada</i>–associated adverse reactions.

(continued)

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

Generic name Brand name (Company)	Warning
	<p>Drugs Affecting Renal Function</p> <ul style="list-style-type: none"> Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of <i>Viread/Stribild/Truvada/Complera/Atripla</i> with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (eg, gentamicin), and high-dose or multiple NSAIDs. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374513.htm</p>
Terconazole vaginal <i>Terazol</i> products (Janssen Pharmaceuticals)	<p>WARNINGS</p> <ul style="list-style-type: none"> Anaphylaxis and toxic epidermal necrolysis have been reported during terconazole therapy. Terazol therapy should be discontinued if anaphylaxis or toxic epidermal necrolysis develops. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience. New section added.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372714.htm</p>
Tocilizumab <i>Actemra</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Laboratory Parameters</p> <ul style="list-style-type: none"> Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended modifications based on ANC results. Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. <p>Hypersensitivity Reactions, Including Anaphylaxis</p> <ul style="list-style-type: none"> Hypersensitivity reactions, including anaphylaxis, have been reported in association with <i>Actemra</i> and anaphylactic events with a fatal outcome have been reported with intravenous infusion of <i>Actemra</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm352022.htm</p>
Tranexamic acid <i>Lysteda</i> (Ferring Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <p>Thromboembolic Risk</p> <ul style="list-style-type: none"> Using combination hormonal contraception <p>WARNINGS AND PRECAUTIONS</p> <p>Thromboembolic Risk</p> <p>Concomitant Use of Hormonal Contraceptives</p> <ul style="list-style-type: none"> Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because <i>Lysteda</i> is antifibrinolytic, the risk of venous thromboembolism, as well as arterial thromboses such as stroke, may increase further when hormonal contraceptives are administered with <i>Lysteda</i>. This is of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age. Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of <i>Lysteda</i>, and there are no clinical trial data on the risk of thrombotic events with the concomitant use of <i>Lysteda</i> with hormonal contraceptives. However, there have been US postmarketing reports of venous and arterial thrombotic events in women who have used <i>Lysteda</i> concomitantly with combination hormonal contraceptives. For this reason, concomitant use of <i>Lysteda</i> with combination hormonal contraceptives is contraindicated.

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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
	<p>DRUG INTERACTIONS</p> <p>Hormonal Contraceptives</p> <ul style="list-style-type: none"> Because <i>Lysteda</i> is antifibrinolytic, concomitant use of hormonal contraception and <i>Lysteda</i> may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. For this reason, concomitant use of <i>Lysteda</i> with combination hormonal contraceptives is contraindicated. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm255213.htm</p>
Trimethoprim/sulfamethoxazole <i>Septra</i> & <i>Septra DS</i> (Monarch Pharmaceuticals)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> In patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides. <p>WARNINGS</p> <ul style="list-style-type: none"> Embryofetal Toxicity: 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. Hypersensitivity and Other Fatal Reactions: Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including SJS, TEN, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Thrombocytopenia: - Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole/trimethoprim. Adjunctive Treatment with Leucovorin for <i>Pneumocystis jiroveci</i> pneumonia: Treatment failure and excess mortality were observed when trimethoprim-sulfamethoxazole was used concomitantly with leucovorin for the treatment of HIV-positive patients with <i>P. jiroveci</i> pneumonia in a randomized placebo-controlled trial. <p>PRECAUTIONS</p> <ul style="list-style-type: none"> Hypoglycemia: – Cases of hypoglycemia in non-diabetic patients treated with sulfamethoxazole/trimethoprim are seen rarely, usually occurring after a few days of therapy. Phenylalanine metabolism: - Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction. Porphyria and Hypothyroidism: - As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction. <p>Use in the Treatment of and Prophylaxis for <i>P. jiroveci</i> Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS):</p> <ul style="list-style-type: none"> AIDS patients may not tolerate or respond to <i>Septra</i> in the same manner as non-AIDS patients. Co-administration of <i>Septra</i> and leucovorin should be avoided with <i>P. jiroveci</i> pneumonia Electrolyte Abnormalities: High dosage of trimethoprim, as used in patients with <i>P. jiroveci</i> pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. <p>Drug Interactions</p> <ul style="list-style-type: none"> Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when <i>Septra</i> is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2. Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

(continued)

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

Generic name Brand name (Company)	Warning
	<ul style="list-style-type: none"> • There have been reports of marked but reversible nephrotoxicity with co-administration of <i>Sepra</i> and cyclosporine in renal transplant recipients. • Increased digoxin blood levels can occur with concomitant <i>Sepra</i> therapy, especially in elderly patients. Serum digoxin levels should be monitored. • Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin. • Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if <i>Sepra</i> is prescribed. • The efficacy of tricyclic antidepressants can decrease when co-administered with <i>Sepra</i>. • <i>Sepra</i> potentiates the effect of oral hypoglycemics that are metabolized by CYP2C8 (eg, pioglitazone, repaglinide, and rosiglitazone) or CYP2C9 (eg, glipizide and glyburide) or eliminated renally via OCT2 (eg, metformin). Additional monitoring of blood glucose may be warranted. • In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin, have also been reported. • In the literature, 3 cases of hyperkalemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and an angiotensin-converting enzyme (ACE) inhibitor. <p>Carcinogenesis, Metagenesis, Impairment of Fertility</p> <p>Carcinogenesis</p> <ul style="list-style-type: none"> • Sulfamethoxazole was not carcinogenic when assessed in a 26-week tumorigenic mouse (Tg-rasH2) study at doses up to 400 mg/kg/day sulfamethoxazole; equivalent to 2.4-fold the human systemic exposure (at a daily dose of 800 mg sulfamethoxazole bid). <p>Mutagenesis</p> <ul style="list-style-type: none"> • In vitro reverse mutation bacterial tests according to the standard protocol have not been performed with sulfamethoxazole and trimethoprim in combination. <p>Pregnancy</p> <p>Impairment of Fertility</p> <ul style="list-style-type: none"> • Doses roughly 2 times the recommended human daily dose on a body surface area basis. <p>Teratogenic Effects: Pregnancy Category D</p> <ul style="list-style-type: none"> • Human Data: While there are no large prospective, well-controlled studies in pregnant women and their babies, some retrospective epidemiologic studies suggest an association between first trimester exposure to sulfamethoxazole/trimethoprim with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular abnormalities, urinary tract defects, oral clefts, and club foot. • Animal Data: In rats, oral doses of either 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palates. <p>Nursing Mothers</p> <ul style="list-style-type: none"> • Levels of trimethoprim/sulfamethoxazole in breast milk are approximately 2%-5% of the recommended daily dose for infants over 2 months of age. <p>Pediatric Use</p> <ul style="list-style-type: none"> • <i>Sepra</i> is contraindicated for pediatric patients younger than 2 months of age. <p>ADVERSE REACTIONS</p> <p>Genitourinary</p> <ul style="list-style-type: none"> • Nephrotoxicity in association with cyclosporine.

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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
	<p>Musculoskeletal</p> <ul style="list-style-type: none"> Isolated cases of rhabdomyolysis have been reported with <i>Sepra</i>, mainly in AIDS patients. <p>Miscellaneous</p> <p>Postmarketing Experience</p> <p>The following adverse reactions have been identified during post-approval use of trimethoprim-sulfamethoxazole. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:</p> <ul style="list-style-type: none"> Thrombotic thrombocytopenia purpura Idiopathic thrombocytopenic purpura QT prolongation resulting in ventricular tachycardia and torsade de pointes <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm370057.htm</p>
Valsartan <i>Diovan</i> (Novartis)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Do not coadminister aliskiren with <i>Diovan</i> in patients with diabetes <p>WARNINGS AND PRECAUTIONS</p> <p>Fetal Toxicity</p> <ul style="list-style-type: none"> Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue <i>Diovan</i> as soon as possible. <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on <i>Diovan</i> and other agents that affect the RAS. Do not coadminister aliskiren with <i>Diovan</i> in patients with diabetes. Avoid use of aliskiren with <i>Diovan</i> in patients with renal impairment (GFR <60 mL/min). <p>USE IN SPECIFIC POPULATIONS</p> <ul style="list-style-type: none"> Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue <i>Diovan</i> as...[sic] <p>Pediatric Use</p> <p>Neonates with a history of in utero exposure to <i>Diovan</i>: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262225.htm</p>
ZIV-aflibercept <i>Zaltrap</i> (sanofi-aventis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Proteinuria</p> <ul style="list-style-type: none"> Monitor proteinuria by urine dipstick analysis and/or urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria during <i>Zaltrap</i> therapy. Patients with a dipstick of =2+ for protein or a UPCR greater than 1 should undergo a 24-hour urine collection. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374591.htm</p>

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