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): March 16, 2014 through April 15, 2014

Albiglutide – Tanzeum (GlaxoSmithKline)	
<i>Comparative agents:</i>	Exenatide, liraglutide
<i>Indication:</i>	Improve glycemic control, along with diet and exercise, in adults with type 2 diabetes
<i>Mechanism of action:</i>	Glucagon-like peptide-1 receptor (GLP-1) agonist
<i>Common adverse effects:</i>	Diarrhea, nausea, and injection site reactions
<i>Dosage form & strength:</i>	Injection; 30 mg, 50 mg single-dose pen
<i>Product labeling:</i>	https://www.gsksource.com/gskprm/htdocs/documents/TANZEUM-PI-MG-IFU-COMBINED.PDF
Apremilast – Otezla (Celgene)	
<i>Comparative agents:</i>	Roflumilast
<i>Indication:</i>	Treatment of adult patients with active psoriatic arthritis (PsA)
<i>Mechanism of action:</i>	Inhibition of phosphodiesterase 4
<i>Common adverse effects:</i>	Diarrhea, nausea, and headache
<i>Dosage form & strength:</i>	Tablets; 10 mg, 20 mg, and 30 mg
<i>Product labeling:</i>	http://www.otezla.com/otezla-prescribing-information.pdf
Coagulation factor IX (recombinant) – Alprolix (Biogen)	
<i>Comparative agents:</i>	Coagulation factor IX
<i>Indication:</i>	Control and prevent bleeding episodes, manage bleeding during surgical procedures, and prevent or reduce the frequency of bleeding episodes (prophylaxis)
<i>Mechanism of action:</i>	Replacement clotting factor
<i>Common adverse effects:</i>	Headache and oral paresthesia
<i>Dosage form & strength:</i>	Injection; 500, 1000, 2000, or 3000 IU vials
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM391049.pdf

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Grass pollen allergen extract – *Oralair* (Stallergenes)

<i>Comparative agents:</i>	Sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass mixed pollens allergen extract
<i>Indication:</i>	Allergic rhinitis with or without conjunctivitis that is induced by certain grass pollens in people ages 10 through 65 years
<i>Mechanism of action:</i>	Unknown; desensitization process
<i>Common adverse effects:</i>	Throat irritation, oral pruritis, ear pruritis, tongue pruritis, oropharyngeal pain, pharyngeal edema, oral paraesthesia or hypoesthesia, abdominal pain, cough, dyspepsia, stomatitis, urticarial, and edema of the lip, tongue, and mouth
<i>Dosage form & strength:</i>	Sublingual tablet; 100 IR and 300 IR
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM391580.pdf

Miltefosine – *Impavido* (Paladin Labs)

<i>Comparative agents:</i>	Amphotericin B, paromomycin
<i>Indication:</i>	Treatment of adults and adolescents ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for treatment of visceral leishmaniasis due to <i>Leishmania donovani</i> ; cutaneous leishmaniasis due to <i>Leishmania braziliensis</i> , <i>Leishmania guyanensis</i> , and <i>Leishmania panamensis</i> ; and mucosal leishmaniasis due to <i>Leishmania braziliensis</i>
<i>Mechanism of action:</i>	Unknown; interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function), and apoptosis-like cell death
<i>Common adverse effects:</i>	Nausea, vomiting, diarrhea, headache, decreased appetite, dizziness, abdominal pain, pruritus, somnolence, elevated transaminases, and elevated creatinine
<i>Dosage form & strength:</i>	Capsule; 50 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204684s000lbl.pdf

Naloxone hydrochloride – *Evzio* (Kaleo)

<i>Comparative agents:</i>	Naloxone
<i>Indication:</i>	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
<i>Mechanism of action:</i>	Opioid antagonist
<i>Common adverse effects:</i>	Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest
<i>Dosage form & strength:</i>	Pre-filled auto-injector: 0.4 mg/0.4 mL
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205787Orig1s000lbl.pdf

Oxycodone hydrochloride & acetaminophen – *Xartemis XR* (Mallinckrodt)

<i>Comparative agents:</i>	Individual ingredients
<i>Indication:</i>	Management of acute pain severe to require opioid treatment and for which alternative treatment options are inadequate
<i>Mechanism of action:</i>	Opioid agonist – mu receptor selective; non-opioid, non-salicylate analgesic, and antipyretic
<i>Common adverse effects:</i>	Nausea, dizziness, headache, vomiting, constipation, and somnolence
<i>Dosage form & strength:</i>	Extended-release tablets; 7.5 mg / 325 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204031s000lbl.pdf

Timothy grass pollen allergen extract – <i>Grastek</i> (Merck)	
<i>Comparative agents:</i>	Sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass mixed pollens allergen extract
<i>Indication:</i>	Treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. It is approved for use in persons 5 through 65 years of age.
<i>Mechanism of action:</i>	Unknown; desensitization process
<i>Common adverse effects:</i>	Ear pruritus, oral pruritus, tongue pruritus, mouth edema, throat irritation
<i>Dosage form & strength:</i>	Sublingual tablet; 2800 BAUs
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergens/UCM393184.pdf

Table 2. New dosage forms and indications approved by the FDA: March 16, 2014 through April 15, 2014

Generic name	Brand name (Company)	Indication and comments
New dosage forms/ strength/route of administration		
Acetaminophen – Prescription combination products	Various	FDA published two Federal Register notices to formally withdraw the applications for all prescription combination drug products that contain more than 325 mg of acetaminophen per tablet, capsule, or other dosage unit. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm390509.htm
New indications		
Apixaban	<i>Eliquis</i> (Bristol-Myers Squibb)	Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.
Dabigatran	<i>Pradaxa</i> (Boehringer Ingelheim)	Treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5 to 10 days; reduce the risk of recurrence of DVT and PE in patients who have been previously treated
Esomeprazole	<i>Nexium 24HR</i> (Pfizer)	Switched from prescription to nonprescription status.
Omalizumab	<i>Xolair</i> (Novartis)	Treatment of chronic idiopathic urticaria
Topiramate	<i>Topamax</i> (Janssen)	Prophylaxis of migraine headaches in adolescents ages 12 to 17

Table 3. Agents pending FDA approval: March 16, 2014 through April 15, 2014

Generic name	Brand name (Company)	Indication and comments
Recommended for approval by an FDA advisory panel		
Dalbavancin	<i>Dalvance</i> (Durata Therapeutics)	Unanimously recommended for approval for the treatment of acute bacterial skin and skin structure infections caused by susceptible Gram-positive bacteria, including methicillin-resistant <i>Staphylococcus aureus</i>
Insulin human [rDNA origin]	<i>Afrezza</i> (MannKind Corporation)	Recommended for approval to improve glycemic control in adults with type 1 diabetes (13 to 1) and type 2 diabetes (14 to 0). Prescription Drug User Fee Act (PDUFA) date changed to July 15, 2014.
Tedizolid	(Cubist)	Unanimously recommended for approval for the treatment of acute bacterial skin infections
Recommended for NON- approval by an FDA advisory panel		
Serelaxin	<i>Reasanx</i> (Novartis)	Cardiovascular and Renal Drug Advisory Committee voted (11-0) against approval for the treatment of acute heart failure
Agents scheduled for review by an FDA advisory panel		
Morphine sulfate & oxycodone hydrochloride	<i>Moxduo</i> (QRx Pharma)	Management of moderate to severe acute pain where the use of an opioid analgesic is appropriate
Naloxegol	(Nektar/ AstraZeneca)	Treatment of opioid induced constipation

Table 4. New drug / biologics license applications filed by manufacturer: March 16, 2014 through April 15, 2014

Generic name Brand name (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Daclatasvir / asunaprevir (Bristol-Myers Squibb)	Sofosbuvir	Treatment of hepatitis C	NS5A replication inhibitor and NS3 protease inhibitor	Headache, diarrhea, asthenia	Oral	Breakthrough therapy designation for treatment of genotype 1b chronic hepatitis C infection; with all oral daclatasvir dual investigational regimens
Soluble ferric pyrophosphate citrate <i>Triferic</i> (Rockwell Medical)	Injectable irons	Iron replacement for chronic kidney disease patients with iron deficiency that are receiving hemodialysis	Iron replacement	Similar to dialysate	Mixed with dialysate	Unique compound that delivers replacement iron to the patient during their hemodialysis sessions.

Table 5. Supplemental applications filed by manufacturer: March 16, 2014 through April 15, 2014

Generic name	Brand name (Company)	Comments
Enzalutamide	<i>Xtandi</i> (Astellas & Medivation)	Treatment of men with metastatic castration-resistant prostate cancer who have not received chemotherapy.
Ibrutinib	<i>Imbruvica</i> (Janssen)	Treatment of relapsed or refractory chronic lymphocytic leukemia (CLL)

Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a

Generic Name Brand Name (Company)	Warning
Anagrelide hydrochloride <i>Agrylin</i> (Shire US)	<p>WARNINGS</p> <p>...added paragraphs:</p> <p>Anagrelide increases the QTc interval of the electrocardiogram and increases the heart rate in healthy volunteers. Anagrelide should not be used in patients with known risk factors for QT interval prolongation, such as congenital long QT syndrome, a known history of acquired QTc prolongation, medicinal products that can prolong QTc interval, and hypokalemia.</p> <p>In patients with heart failure, bradyarrhythmias, or electrolyte abnormalities, consider periodic monitoring with electrocardiograms.</p> <p>In patients with cardiac disease, use <i>Agrylin</i> only when the benefits outweigh the risks.</p> <p>PRECAUTIONS</p> <p>Hypotension: In 9 subjects receiving a single 5 mg dose of anagrelide, standing blood pressure fell an average of 22/15 mm Hg, usually accompanied by dizziness. Only minimal changes in blood pressure were observed following a dose of 2 mg.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm175918.htm</p>
Asparaginase <i>Erwinia chrysanthemi</i> <i>Erwinaze</i> (EUSA Pharma)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypersensitivity Reactions</p> <p>Grade 3 and 4 hypersensitivity reactions after the use of <i>Erwinaze</i> have occurred in 5% of patients in clinical trials.</p> <p>Anaphylaxis after the use of <i>Erwinaze</i> has occurred in 0.8% of patients in clinical trials.</p> <p>Glucose Intolerance</p> <p>Glucose intolerance has been reported with <i>Erwinaze</i> therapy in 4% of patients in clinical trials.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392222.htm</p>
Azathioprine <i>Imuran</i> (Prometheus Laboratories)	<p>WARNINGS</p> <p>Serious Infections - Progressive Multifocal Leukoencephalopathy.</p> <p>Cases of JC virus-associated infection resulting in progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with immunosuppressants, including <i>Imuran</i>. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. Consider the diagnosis of PML in any patient presenting with new-onset neurological manifestations and consider consultation with a neurologist as clinically indicated.</p> <p>Consider reducing the amount of immunosuppression in patients who develop PML. In transplant patients, consider the risk that the reduced immunosuppression represents to the graft.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258794.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Boceprevir <i>Victrelis</i> (Merck)	<p>WARNINGS AND PRECAUTIONS</p> <p>Pancytopenia (Use with Ribavirin and Peginterferon Alfa)</p> <p>Serious cases of pancytopenia have been reported postmarketing in patients receiving <i>Victrelis</i> in combination with peginterferon alfa and ribavirin. Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at treatment weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. Refer to the Package Inserts for ribavirin and peginterferon alfa for guidelines for discontinuation of therapy based on laboratory parameters.</p> <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <p>Blood and Lymphatic System Disorders: agranulocytosis, pancytopenia, thrombocytopenia</p> <p>Infections and Infestations: pneumonia, sepsis</p> <p>PATIENT COUNSELING INFORMATION</p> <p>Pancytopenia</p> <p>Patients should be informed that serious cases of pancytopenia have been reported during postmarketing when <i>Victrelis</i> was administered with peginterferon alfa and ribavirin. Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303600.htm</p>
Cabazitaxel <i>Jevtana</i> (sanofi aventis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Gastrointestinal Disorders</p> <p>Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with <i>Jevtana</i>. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, anti-platelet therapy, or anti-coagulants, and patients with a prior history of pelvic radiotherapy, adhesions, ulceration, and GI bleeding. Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious GI toxicity and should be evaluated and treated promptly. <i>Jevtana</i> treatment delay or discontinuation may be necessary.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392358.htm</p>
Calcitonin-salmon <i>Miacalcin</i> (Novartis)	<p>Information from a meta-analysis of 21 randomized, controlled studies was added to the Warnings and Precaution and Adverse Reactions sections regarding the increased risk of malignancies with calcitonin-salmon therapy.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm190771.htm</p>
Carbidopa <i>Lodosyn</i> (Valeant Pharmaceuticals North America)	<p>WARNINGS</p> <p>The addition of <i>Lodosyn</i> with carbidopa-levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, <i>Lodosyn</i> does not decrease the adverse reactions due to the central effects of levodopa. Because <i>Lodosyn</i> permits more levodopa to reach the brain and more dopamine to be formed, certain adverse central nervous system (CNS) effects, eg, dyskinesias (involuntary movements), may occur at lower dosages and sooner with levodopa in combination with <i>Lodosyn</i> than with levodopa alone.</p> <p>Falling Asleep During Activities of Daily Living and Somnolence</p> <p>Neuroleptic Malignant Syndrome (NMS) section revised into Hyperpyrexia and Confusion</p> <p>PRECAUTIONS</p> <p>Sections added:</p> <p>Impulse Control/Compulsive Behaviors; Hallucinations/Psychotic Like Behavior; Dyskinesia; Depression; Melanoma Information for Patients</p> <p>DRUG INTERACTIONS</p> <p><i>Lodosyn</i> and iron salts or multivitamins containing iron salts should be coadministered with caution. Iron salts can form chelates with levodopa and carbidopa and consequently reduce the bioavailability of carbidopa and levodopa.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm388773.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Eltrombopag <i>Promacta</i> (GlaxoSmithKline)	<p>BOXED WARNING</p> <p>WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C</p> <p>In patients with chronic hepatitis C, <i>Promacta</i> in combination with interferon and ribavirin may increase the risk of hepatic decompensation.</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Hepatic Decompensation in Patients With Chronic Hepatitis C</p> <p>Revised to include the risk of hepatic decompensation.</p> <p>Hepatotoxicity</p> <p><i>Promacta</i> can cause liver enzyme elevations. Measure serum ALT, AST, and bilirubin prior to initiation of <i>Promacta</i>, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. <i>Promacta</i> inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia.</p> <p>Bone Marrow Reticulin Formulation ...section removed.</p> <p>Laboratory Monitoring...section removed.</p> <p>ADVERSE REACTIONS</p> <p>Hepatic Decompensation in Patients With Chronic Hepatitis C</p> <p>PATIENT COUNSELING INFORMATION</p> <p>Confusion</p> <p>Swelling of the stomach area (abdomen)</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm207394.htm</p>
Estradiol transdermal spray <i>Evamist</i> (Ther-Rx Corporation)	<p>CONTRAINDICATIONS</p> <p>Known anaphylactic reaction or angioedema</p> <p>Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Hereditary Angioedema</p> <p>Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.</p> <p>ADVERSE REACTIONS</p> <p>Postmarketing Experiences</p> <p>Skin: Nipple and areola discoloration, usually on the same side of the body as the inner forearm on which <i>Evamist</i> is applied, rash, pruritus, alopecia, urticaria, dry skin, skin discoloration, chloasma</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm279996.htm</p>
Everolimus <i>Afinitor</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Impaired Wound Healing</p> <p>Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of <i>Afinitor</i> in the peri-surgical period.</p> <p>Embryo-fetal Toxicity</p> <p>Based on the mechanism of action, <i>Afinitor</i> can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. 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. Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception while using <i>Afinitor</i> and for up to 8 weeks after ending treatment.</p> <p>ADVERSE REACTIONS</p> <p>Clinical Study Experience in Advanced Pancreatic Neuroendocrine Tumors: irregular menstruation... percentage increased ... occurred in 5 of 46 (11%)</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258494.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Ezetimibe/ simvastatin <i>Vytorin</i> (Merck)	<p>CONTRAINDICATIONS</p> <p>Added...cobicistat-containing products</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Myopathy/Rhabdomyolysis</p> <p>Drug Interactions... paragraph added</p> <p>DRUG INTERACTIONS</p> <p>Added... cobicistat-containing products to the existing list of strong CYP3A4 inhibitors</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208609.htm</p>
Fluconazole <i>Diflucan</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <p>Coadministration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as erythromycin are contraindicated in patients receiving fluconazole.</p> <p>WARNINGS</p> <p>Patients with deep seated fungal infections who develop rashes during treatment with <i>Diflucan</i> should be monitored closely and the drug discontinued if lesions progress. Fluconazole should be discontinued in patients treated for superficial fungal infection who develop a rash that may be attributed to fluconazole.</p> <p>PRECAUTIONS</p> <p>Drug Interactions</p> <p>Cyclosporine: <i>Diflucan</i> significantly increases cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving <i>Diflucan</i> and cyclosporine. This combination may be used by reducing the dosage of cyclosporine depending on cyclosporine concentration.</p> <p>Quinidine: Although not studied in vitro or in vivo, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of torsades de pointes. Coadministration of fluconazole and quinidine is contraindicated.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262570.htm</p>
Golimumab <i>Simponi Aria</i> (Janssen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Serious Infections - Tuberculosis</p> <p>Cases of active tuberculosis have occurred in patients treated with the subcutaneous formulation of golimumab during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.</p> <p>Vaccinations/Therapeutic Infectious Agents</p> <p>Live Vaccines</p> <p>Patients treated with <i>Simponi Aria</i> may receive vaccinations, except for live vaccines. In patients receiving anti-TNF therapy, limited data are available on the response to live vaccination, or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.</p> <p>Therapeutic Infectious Agents</p> <p>Other uses of therapeutic infectious agents such as live attenuated bacteria (eg, BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with <i>Simponi Aria</i>.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm388774.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Ketoconazole <i>Nizoral</i> (Janssen Pharmaceuticals)	BOXED WARNING Addition of contraindicated medications...methadone, disopyramide, dronedarone, ranolazine. WARNINGS QT Prolongation and Drug Interaction Leading to QT Prolongation Addition of contraindicated medications...methadone, disopyramide, dronedarone, ranolazine. PRECAUTIONS Drug Interactions ...entire section revised http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm364157.htm
Lovastatin <i>Mevacor</i> (Merck)	CONTRAINDICATIONS Added...cobicistat-containing products WARNINGS Strong inhibitors of CYP3A4: Added...cobicistat-containing products PRECAUTIONS CYP3A4 Interactions Added...cobicistat-containing products http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm389714.htm
Maraviroc <i>Selzentry</i> (ViiV Healthcare)	WARNINGS AND PRECAUTIONS Cardiovascular Events Caution should be used when administering <i>Selzentry</i> in patients with a history of or risk factors for postural hypotension, cardiovascular comorbidities, or on concomitant medication known to lower blood pressure. Patients with cardiovascular comorbidities could be at increased risk of cardiovascular adverse events triggered by postural hypotension. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm215506.htm
Menotropins for injection <i>Menopur</i> (Ferring Pharmaceuticals)	CONTRAINDICATIONS Pregnancy: May cause fetal harm when administered to a pregnant woman; is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the woman becomes pregnant while taking this drug, the woman should be apprised of the potential hazard to a fetus. WARNINGS AND PRECAUTIONS: Sections updated Ovarian Hyperstimulation Syndrome (OHSS) Pulmonary and Vascular Complications Ovarian Torsion Multi-fetal Gestation and Birth Congenital Malformations Ectopic Pregnancy Spontaneous Abortion Ovarian Neoplasms http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm389227.htm
Naproxen/ esomeprazole magnesium <i>Vimovo</i> (Horizon Pharma)	WARNINGS AND PRECAUTIONS Renal Effects Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion; those taking diuretics, ACE inhibitors, or angiotensin II receptor antagonists; and the elderly. Laboratory Tests Health care providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (eg, for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262248.htm

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Palonosetron hydrochloride <i>Aloxi</i> (EISAI)	WARNINGS AND PRECAUTIONS Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT ₃ receptor antagonists. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm388768.htm
Rifaximin <i>Xifaxan</i> (Salix Pharmaceuticals)	WARNINGS AND PRECAUTIONS Concomitant use with P-glycoprotein Inhibitors Concomitant administration of drugs that are P-glycoprotein inhibitors with rifaximin can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor such as cyclosporine is needed. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-glycoprotein inhibitors may further increase the systemic exposure to rifaximin. DRUG INTERACTIONS Concomitant P-glycoprotein inhibitors An in vitro study suggested that rifaximin is a substrate of P-glycoprotein. Co-administration of cyclosporine, a potent P-glycoprotein inhibitor, with rifaximin resulted in 83-fold and 124-fold increases in rifaximin mean C _{max} and AUC in healthy subjects. The clinical significance of this increase in systemic exposure is unknown. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392729.htm
Rivaroxaban <i>Xarelto</i> (Janssen)	BOXED WARNING Optimal timing between the administration of <i>Xarelto</i> and neuraxial procedures is not known. WARNINGS AND PRECAUTIONS Spinal/Epidural Anesthesia or Puncture To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm367392.htm
Sevoflurane, volatile liquid for inhalation <i>Ultane & Ultane</i> <i>NovaPlus</i> (AbbVie)	WARNINGS Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering sevoflurane to susceptible patients (eg, patients with congenital long QT syndrome or patients taking drugs that can prolong the QT interval). http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319035.htm
Sildenafil <i>Revatio & Viagra</i> (Pfizer)	WARNINGS AND PRECAUTIONS Effects on the Eye Based on published literature, the annual incidence of non-arteritic anterior ischemic optic neuropathy (NAION) is 2.5-11.8 cases per 100,000 in males aged ≥ 50. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319416.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm200593.htm

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Simvastatin <i>Zocor</i> (Merck)	<p>CONTRAINDICATIONS</p> <p>Added...cobicistat-containing products</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Myopathy/Rhabdomyolysis - Drug Interactions... paragraph added</p> <p>DRUG INTERACTIONS</p> <p>Added... cobicistat-containing products to the existing list of strong CYP3A4 inhibitors</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208610.htm</p>
Sitagliptin/ simvastatin <i>Javisync</i> (Merck)	<p>CONTRAINDICATIONS</p> <p>Added...cobicistat-containing products</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Myopathy/Rhabdomyolysis</p> <p>Drug Interactions... paragraph added</p> <p>DRUG INTERACTIONS</p> <p>Added... cobicistat-containing products to the existing list of strong CYP3A4 inhibitors</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm323856.htm</p>
Sodium iodide I-131 solution therapeutic (Mallinckrodt)	<p>CONTRAINDICATIONS</p> <p>Breastfeeding</p> <p>ADVERSE REACTIONS</p> <p>The following adverse reactions have been reported with doses of sodium iodide I-131 used in the treatment of benign disease, such as hyperthyroidism:</p> <p>Sialadenitis, iododerma, hypothyroidism, hyperthyroidism, thyrotoxic crisis, hypoparathyroidism, and local [sic]</p> <p>The following adverse reactions have been reported with doses of sodium iodide I-131 used in the treatment of malignant disease:</p> <p>Solid cancers, nausea, vomiting, and congenital hypothyroidism</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm296271.htm</p>
Sulfasalazine <i>Azulfidine</i> (Pfizer)	<p>WARNINGS</p> <p>Serious infections, including fatal sepsis and pneumonia, have been reported. Some infections were associated with agranulocytosis, neutropenia, or myelosuppression. Discontinue <i>Azulfidine</i> if a patient develops a serious infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with <i>Azulfidine</i>. For a patient who develops a new infection during treatment with <i>Azulfidine</i>, perform a prompt and complete diagnostic workup for infection and myelosuppression. Caution should be exercised when considering the use of sulfasalazine in patients with a history of recurring or chronic infections or with underlying conditions or concomitant drugs which may predispose patients to infections.</p> <p>Severe hypersensitivity reactions may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome (ie, pseudomononucleosis), hematological abnormalities (including hematophagic histiocytosis), and/or pneumonitis including eosinophilic infiltration.</p> <p>PRECAUTIONS</p> <p>Drug/Laboratory Test Interactions</p> <p>Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.</p> <p>ADVERSE REACTIONS</p> <p>Postmarketing Reports</p> <p>Blood dyscrasias: pseudomononucleosis; Cardiac disorders: myocarditis; Metabolism and nutrition system disorders: folate deficiency; Renal and urinary disorders: nephrolithiasis; Respiratory, thoracic, and mediastinal disorders: oropharyngeal pain</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm335424.htm</p>

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Tacrolimus extended-release capsules <i>Astagraf XL</i> (Astellas Pharma)	WARNINGS AND PRECAUTIONS Use with CYP3A4 Inhibitors and Inducers QT Prolongation ...added section Gastrointestinal Perforation ...added section ADVERSE REACTIONS Added bullet point...Gastrointestinal Perforation DRUG INTERACTIONS Dose adjustments may be needed along with frequent monitoring of tacrolimus whole blood trough concentrations when <i>Astagraf XL</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. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm388770.htm
Tofacitinib <i>Xeljanz</i> (Pfizer)	WARNINGS AND PRECAUTIONS Non-Melanoma Skin Cancer Non-melanoma skin cancers (NMSCs) have been reported in patients treated with <i>Xeljanz</i> . Periodic skin examination is recommended for patients who are at increased risk for skin cancer. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392730.htm
Tolvaptan <i>Samsca</i> (Otsuka)	CONTRAINDICATIONS Hypersensitivity...section added ADVERSE REACTIONS Postmarketing Experience Immune System Disorders: Hypersensitivity reactions including anaphylactic shock and rash generalized. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm294226.htm
Trastuzumab <i>Herceptin</i> (Genentech)	WARNINGS AND PRECAUTIONS Cardiomyopathy Results from two studies were added to this section. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392225.htm
Urofollitropin for injection <i>Bravelle</i> (Ferring Pharmaceuticals)	CONTRAINDICATIONS Pregnancy...may cause fetal harm when administered to a pregnant woman; is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the woman becomes pregnant while taking this drug, the woman should be apprised of the potential hazard to a fetus. WARNINGS AND PRECAUTIONS: Sections updated Ovarian Hyperstimulation Syndrome (OHSS) Pulmonary and Vascular Complications Ovarian Torsion Multi-fetal Gestation and Birth Congenital Malformations Ectopic Pregnancy Spontaneous Abortion Ovarian Neoplasms http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm389226.htm

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Table 6. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Generic Name Brand Name (Company)	Warning
Valproic acid <i>Stavzor</i> (Noven Therapeutics)	<p>BOXED WARNING</p> <p>Life-Threatening Adverse Reactions: Hepatotoxicity</p> <p>Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months.</p> <p>Populations at increased risk include: children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease; incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups; and patients with mitochondrial disease (patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ [POLG] gene [eg, Alpers Huttenlocher Syndrome]).</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Hepatotoxicity: General Information on Hepatotoxicity; Patients with Known or Suspected Mitochondrial Disease</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360495.htm</p>
Vemurafenib <i>Zelboraf</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypersensitivity Reactions - addition of DRESS Syndrome</p> <p>ADVERSE REACTIONS</p> <p>addition of Hypersensitivity Reactions</p> <p>Postmarketing Experience</p> <p>addition of... progression of a pre-existing chronic myelomonocytic leukemia with NRAS mutation.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm364374.htm</p>

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