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: May 16, 2015 through July 12, 2015

Eluxadoline – *Viberzi* (Forest Pharmaceuticals)

<i>Comparative agents:</i>	Loperamide
<i>Indication:</i>	Adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D)
<i>Mechanism of action:</i>	Mu-opioid receptor agonist
<i>Common adverse effects:</i>	Constipation, nausea, and abdominal pain
<i>Dosage form & strength:</i>	Tablet; 75 and 100 mg
<i>Product labeling:</i>	www.viberzi.com

Cangrelor – *Kengreal* (The Medicine Company)

<i>Comparative agents:</i>	Clopidogrel, prasugrel ticagrelor, ticlopidine
<i>Indication:</i>	Adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients in who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor
<i>Mechanism of action:</i>	P2Y12 platelet inhibitor
<i>Common adverse effects:</i>	Bleeding
<i>Dosage form & strength:</i>	Injectable; 50 mg/10 mL vial
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204958lbl.pdf

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Table 1. New drugs approved by the US Food and Drug Administration: May 16, 2015 through July 12, 2015 (CONT.)

Lumacaftor/ivacaftor – <i>Orkambi</i> (Vertex Pharmaceuticals)	
<i>Comparative agents:</i>	Ivacaftor
<i>Indication:</i>	Treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the transmembrane conductance regulator (CFTR) gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.
<i>Mechanism of action:</i>	Transmembrane conductance regulator potentiator
<i>Common adverse effects:</i>	Dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, influenza
<i>Dosage form & strength:</i>	Tablet; 200 mg/125 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206038Orig1s000lbl.pdf
Sacubitril/valsartan – <i>Entresto</i> (Novartis)	
<i>Comparative agents:</i>	Valsartan
<i>Indication:</i>	Reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction
<i>Mechanism of action:</i>	Neprilysin inhibitor and angiotensin II receptor blocker
<i>Common adverse effects:</i>	Hypotension, hyperkalemia, cough, dizziness, and renal failure
<i>Dosage form & strength:</i>	Tablet; 24/26 mg, 49/51 mg, 97/103 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf
Tiotropium bromide/olodaterol – <i>Stiolto Respimat</i> (Boehringer Ingelheim)	
<i>Comparative agents:</i>	Individual ingredients
<i>Indication:</i>	Long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease
<i>Mechanism of action:</i>	Long-acting muscarinic antagonist and long-acting beta2-adrenergic agonist
<i>Common adverse effects:</i>	Nasopharyngitis, cough, back pain
<i>Dosage form & strength:</i>	Inhaler; 2.5 mcg tiotropium & 2.5 mcg olodaterol
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206756Orig1s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: May 16, 2015 through July 12, 2015

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/route of administration		
Paliperidone	<i>Invega Trinza</i> (Johnson & Johnson)	Longer-acting formulation that allows administration 4 times each year for the treatment of schizophrenia
New indications		
Filgrastim	<i>Neupogen</i> (Amgen)	Treatment of radiation exposure following a nuclear incident
Meropenem	(various)	Treatment of abdominal infections in infants aged 3 months or younger
Rifaximin	<i>Xifaxan</i> (Salix Pharms)	Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adult men and women
Sirolimus	<i>Rapamune</i> (Pf Prism Cv)	Treat lymphangioleiomyomatosis (LAM); sirolimus is the first drug approved to treat the disease.
Topiramate	<i>Qudexy XR</i> (Upsher-Smith)	Children 2 and older who are experiencing partial-onset seizures or tonic-clonic seizures

Table 3. Agents pending FDA approval: May 16, 2015 through July 12, 2015

Generic name	Brand name (Company)	Indication and comments
Complete response letter: more information required		
Hydroxyprogesterone caproate injection	<i>Makena</i> (AMAG Pharmaceuticals)	Single-dose vial by a new third-party manufacturer – request for more information related to manufacturing procedures
Recommended for approval by an FDA advisory panel		
Alirocumab	<i>Praluent</i> (Sanofi/Regeneron Pharmaceuticals)	Use in conjunction with a healthy diet for long-term treatment of adult patients with primary hypercholesterolemia (nonfamilial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes (13 to 3 in favor).
Evolocumab	<i>Repatha</i> (Amgen)	Treat homozygous familial hypercholesterolemia (15 to 0 in favor) or at-risk patients for whom statins are inadequate (11 to 4 in favor).
Flibanserin	<i>Addyi</i> (Sprout)	Treatment of hypoactive sexual desire disorder in premenopausal women; committee vote was 18 to 6 for approval.
Mepolizumab	(GlaxoSmithKline)	Treatment of severe asthma in adults (14 to 0 in favor of approval); committee did not support its use in adolescents (10 to 4 against).
Necitumumab	(Eli Lilly)	Combination with gemcitabine and cisplatin for first-line treatment of patients with locally advanced or metastatic squamous non-small-cell lung cancer; community supported its use but no formal vote was taken at the meeting.
Agents scheduled for review by an FDA advisory panel		
Alirocumab	<i>Praluent</i> (sanofi aventis)	Adjunct to diet for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol, total cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B, triglyceride, and lipoprotein A and to increase high-density lipoprotein cholesterol and apolipoprotein A-1 either in combination with a statin or as monotherapy including in patients who cannot tolerate statins. [July 2015]
Evolocumab	<i>Repatha</i> (Amgen)	Adjunct to diet to reduce low-density lipoprotein cholesterol, total cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B, triglyceride, and lipoprotein A and to increase high-density lipoprotein cholesterol and apolipoprotein A-1 in adults with hyperlipidemia or mixed dyslipidemia either in combination with a statin, statin with other lipid-lowering therapies, or in combination with other lipid-lowering therapies in patients who are statin-intolerant; or as monotherapy or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. [July 2015]
Flibanserin	(Sprout Pharmaceuticals)	Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women [July 2015]
Mepolizumab	(GlaxoSmithKline)	Add-on maintenance treatment in patients 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/microliter at initiation of treatment or blood eosinophils greater than or equal to 300 cells/microliter in the past 12 months [July 2015]

Current FDA-Related Drug Information

Table 4. New drug/biologics license applications filed by manufacturer: May 16, 2015 through July 12, 2015

Generic name <i>Brand name</i> (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Eteplirsen (Sarepta Therapeutics)	Drisapersen	Duchenne muscular dystrophy	Morpholino antisense oligomer that alters the RNA coding to avoid the development of the non-functional dystrophin protein	Injection site reactions	Injection	
Grazoprevir/ elbasvir (Merck)	<i>Harvoni</i> , <i>Viekira Pak</i>	Treatment of hepatitis C in patients with genotypes 1, 4, and 6	NS3/4A protease inhibitor and NS5A replication complex inhibitor	Fatigue, headache, nausea, diarrhea, general weakness	Tablet	FDA Breakthrough Therapy designation
Sodium zirconium cyclosilicate (ZS Pharma)	Sodium polystyrene sulfonate	Treatment of hyperkalemia	Traps potassium ions (ion trap)	Diarrhea, constipation, nausea, vomiting, abdominal pain, abdominal distention, dyspepsia, flatulence, gastric ulcers, gastritis, and frequent bowel movements, arrhythmias, AT prolongation, and urinary tract infections	Oral with food	

Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a

Generic name <i>Brand name</i> (Company)	Warning
Bedaquiline <i>Sirturo</i> (Janssen Therapeutics)	<p>BOXED WARNING [edited] QT Prolongation</p> <ul style="list-style-type: none"> QT prolongation can occur with monotherapy and when used with drugs that prolong the QT interval may cause additive QT prolongation. Discontinue therapy if significant ventricular arrhythmia or if QTcF interval prolongation of greater than 500 ms develops. <p>WARNINGS AND PRECAUTIONS</p> <p>Hepatotoxicity</p> <ul style="list-style-type: none"> More hepatic-related adverse reactions were reported with the use of <i>Sirturo</i> plus other drugs used to treat tuberculosis compared to other drugs used to treat tuberculosis without the addition of <i>Sirturo</i>. Alcohol and other hepatotoxic drugs should be avoided while on <i>Sirturo</i>, especially in patients with impaired hepatic function. Monitor symptoms (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) and laboratory tests (alanine transaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) at baseline, monthly while on treatment, and as needed. Test for viral hepatitis and discontinue other hepatotoxic medications if evidence of new or worsening liver dysfunction occurs. <p>Discontinue if:</p> <ul style="list-style-type: none"> aminotransferase elevations are accompanied by total bilirubin elevation greater than 2 times the upper limit of normal. aminotransferase elevations are greater than 8 times the upper limit of normal. aminotransferase elevations are greater than 5 times the upper limit of normal and persist beyond 2 weeks. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368240.htm</p>

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Bevacizumab <i>Avastin</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Embryo-Fetal Toxicity [section added]</p> <ul style="list-style-type: none"> <i>Avastin</i> may cause fetal harm based on the drug’s mechanism of action and findings from animal studies. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of <i>Avastin</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm287610.htm</p>
Darunavir <i>Prezista</i> (Janssen)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Dronedarone, colchicine, and ranolazine were added to the list of medications to avoid during darunavir therapy. <p>DRUG INTERACTIONS</p> <p>P-gp interactions</p> <ul style="list-style-type: none"> P-gp information added to drug-drug interaction that might increase plasma concentrations of darunavir or other drugs, which could increase or prolong their therapeutic effect and adverse events. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm287579.htm</p>
Emtricitabine, rilpivirine, tenofovir disoproxil fumarate <i>Complera</i> (Gilead Science)	<p>WARNINGS AND PRECAUTIONS</p> <p>Skin and Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the phase 3 clinical trials, treatment-related rashes with at least grade 2 severity were reported in 1% of subjects receiving rilpivirine plus emtricitabine/tenofovir DF. Overall, most rashes were grade 1 or 2 and occurred in the first 4 to 6 weeks of therapy. Discontinue immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis, or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated. <p>ADVERSE REACTIONS - Postmarketing Experience</p> <p>Skin and Subcutaneous Tissue Disorders</p> <ul style="list-style-type: none"> Severe skin and hypersensitivity reactions including DRESS <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm318602.htm</p>
Fingolimod <i>Gilenya</i> (Novartis)	<p>WARNINGS AND PRECAUTIONS</p> <p>Bradyarrhythmia and Atrioventricular Blocks</p> <p>Reduction in Heart Rate</p> <ul style="list-style-type: none"> In controlled clinical trials, adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving <i>Gilenya</i> 0.5 mg and in 0.1% of patients on placebo. <p>Atrioventricular Blocks [section edited]</p> <ul style="list-style-type: none"> Initiation of <i>Gilenya</i> treatment has resulted in transient AV conduction delays. In controlled clinical trials, first-degree and second-degree AV block occurred in some patients after the first dose. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but they occasionally required treatment with atropine or isoproterenol. <p>Infections</p> <p>Risk of Infections</p> <ul style="list-style-type: none"> [added]...a recent CBC (ie, within 6 months or after discontinuation of prior therapy) should be available. [edited]...In MS placebo-controlled trials, the overall rate of infections (72%) with <i>Gilenya</i> was similar to placebo. However, bronchitis, herpes zoster, influenza, sinusitis, and pneumonia were more common in <i>Gilenya</i>-treated patients. Serious infections occurred at a rate of 2.3% in the <i>Gilenya</i> group versus 1.6% in the placebo group.

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

	<p>Herpes Viral Infections [section added]</p> <p>Prior and Concomitant Treatment with Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies [section edited]</p> <p>Varicella Zoster Virus Antibody Testing/Vaccination [section edited]</p> <p>Macular Edema section</p> <ul style="list-style-type: none"> Fingolimod increases the risk of macular edema. Perform an examination of the fundus including the macula in all patients before starting treatment, again 3-4 months after starting treatment, and again at any time after a patient reports visual disturbances while on <i>Gilenya</i> therapy. A dose-dependent increase in the risk of macular edema occurred in the <i>Gilenya</i> clinical development program. <p>Macular Edema in Patients with History of Uveitis or Diabetes Mellitus</p> <ul style="list-style-type: none"> Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during <i>Gilenya</i> therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In addition to the examination of the fundus including the macula prior to treatment and at 3-4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations. <p>Respiratory Effects</p> <ul style="list-style-type: none"> Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with <i>Gilenya</i> as early as 1 month after treatment initiation. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm266123.htm</p>
Interferon alfa-2b, recombinant <i>Intron A</i> (Schering)	<p>WARNINGS</p> <p>Neuropsychiatric Disorders</p> <ul style="list-style-type: none"> If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation or aggressive behavior toward others is identified, discontinue treatment with <i>Intron A</i> and follow the patient closely, with psychiatric intervention as appropriate. Narcotics, hypnotics, or sedatives may be used concurrently with caution and patients should be closely monitored until the adverse effects have resolved. <p>Gastrointestinal Disorders</p> <ul style="list-style-type: none"> <i>Intron A</i> increases the risk of hepatic decompensation and death in patients with cirrhosis. Any patient developing liver function abnormalities during treatment should be monitored closely, and if appropriate treatment should be discontinued. <p>PRECAUTIONS – Laboratory Tests</p> <ul style="list-style-type: none"> Monitor hepatic function with serum bilirubin, ALT, AST, alkaline phosphatase, and LDH (lactate dehydrogenase) at 2, 8, and 12 weeks following initiation of <i>Intron A</i>, then every 6 months while receiving <i>Intron A</i>. Permanently discontinue <i>Intron A</i> for evidence of severe (grade 3) hepatic injury or hepatic decompensation (Child-Pugh score >6 [class B and C]). <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm311115.htm</p>
Lamotrigine <i>Lamictal</i> (GlaxoSmithKline)	<p>BOXED WARNING</p> <ul style="list-style-type: none"> Can cause serious rashes requiring hospitalization and discontinuation of treatment <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm450548.htm</p>

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

Medroxyprogesterone acetate <i>Provera</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Known anaphylactic reaction or angioedema <p>ADVERSE REACTIONS</p> <p>The following adverse reactions have been reported in women taking <i>Provera</i> tablets, without concomitant estrogens treatment:</p> <ul style="list-style-type: none"> Hypersensitivity reactions (eg, anaphylaxis and anaphylactoid reactions, angioedema), rash (allergic) with and without pruritus, change in weight (increase or decrease), pyrexia, edema/fluid retention, fatigue, decreased glucose tolerance <p>The following adverse reactions have been reported with estrogen plus progestin therapy:</p> <ul style="list-style-type: none"> Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm450141.htm</p>
Nonsteroidal anti-inflammatory drugs; non-aspirin (various)	<p>Labeling will be changed to state there is an increased chance of heart attack or stroke.</p> <p>http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery</p>
Peginterferon alfa-2b <i>PegIntron</i> (Schering)	<p>WARNINGS AND PRECAUTIONS</p> <p>Neuropsychiatric Events</p> <ul style="list-style-type: none"> Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior sometimes directed toward others have occurred in patients with and without a previous psychiatric disorder during with interferon alpha products. These drugs should be used with caution in patients with a history of psychiatric disorders. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm311124.htm</p>
Peginterferon alfa-2b <i>Sylatron</i> (Schering)	<p>WARNINGS AND PRECAUTIONS</p> <p>Depression and Other Serious Neuropsychiatric Adverse Reactions</p> <ul style="list-style-type: none"> Permanently discontinue for suicidal or homicidal ideation, aggressive behavior towards others, or other severe or persistent psychiatric symptoms; institute psychiatric intervention and follow-up as appropriate. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Pulmonary fibrosis <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm314604.htm</p>
Pertuzumab <i>Perjeta</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Embryo-Fetal Toxicity [section edited]</p> <ul style="list-style-type: none"> If <i>Perjeta</i> is administered during pregnancy, or if the patient becomes pregnant while receiving this drug or within 7 months following the last dose of <i>Perjeta</i> in combination with trastuzumab, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)]. If <i>Perjeta</i> is administered during pregnancy or if a patient becomes pregnant while receiving <i>Perjeta</i> or within 7 months following the last dose of <i>Perjeta</i> in combination with trastuzumab, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy or within 7 months for <i>Perjeta</i> in combination with trastuzumab prior to conception, to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-6720 [see Patient Counseling Information (17)].

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Table 5. Significant labeling changes or “Dear Health Professional” letters related to safety^a (CONT.)

	<p>USE IN SPECIFIC POPULATIONS</p> <p>Females of Reproductive Potential</p> <ul style="list-style-type: none"> Advise females of reproductive potential to use effective contraception while receiving <i>Perjeta</i> and for 7 months following the last dose of <i>Perjeta</i> in combination with trastuzumab. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm450065.htm</p>
Ribavirin <i>Rebetol</i> (Merck)	<p>Homicidal ideation added to Warnings and Precautions section.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm233679.htm</p>
Rilpivirine <i>Edurant</i> (Janssen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Skin and Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of DRESS, with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. Discontinue immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis, or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated. <p>ADVERSE REACTIONS - Postmarketing Experience</p> <ul style="list-style-type: none"> Skin and Subcutaneous Tissue Disorders: Severe skin and hypersensitivity reactions including DRESS <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360386.htm</p>
Testosterone products (various)	<p>Class warning regarding cardiovascular risk:</p> <p>Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm451075.htm</p>
Vismodegib <i>Erivedge</i> (Genentech)	<p>WARNING: EMBRYO-FETAL TOXICITY</p> <ul style="list-style-type: none"> <i>Erivedge</i> can cause embryo-fetal death or severe birth defects (eg, severe midline defects, missing digits, and other irreversible malformations) when administered to a pregnant woman. <i>Erivedge</i> is embryotoxic, fetotoxic, and teratogenic in animals. Pregnancy testing and monitoring is emphasized and male patients should use condoms, even after a vasectomy, during treatment and for 3 months after the final dose of vismodegib. <p>Blood Donation</p> <ul style="list-style-type: none"> Advise patients not to donate blood or blood products and for 7 months after the final dose of vismodegib. <p>Sperm Donation</p> <ul style="list-style-type: none"> Advise male patients not to donate semen during and for 3 months after the final dose. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm450147.htm</p>

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