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): July 15, 2014 through August 15, 2014

C-1-esterase inhibitor [recombinant] – Ruconest (Salix Pharmaceuticals)	
<i>Comparative agents:</i>	C-1-esterase inhibitor [human]
<i>Indication:</i>	Treatment of acute attacks in adult and adolescent patients with hereditary angioedema
<i>Mechanism of action:</i>	C1-esterase inhibitor replacement
<i>Common adverse effects:</i>	Headache, nausea, and diarrhea
<i>Dosage form & strength:</i>	Injection; 2100 IU
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM405634.pdf
Empagliflozin – Jardiance (Boehringer Ingelheim Pharmaceuticals)	
<i>Comparative agents:</i>	Canagliflozin, Dapagliflozin
<i>Indication:</i>	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
<i>Mechanism of action:</i>	Sodium-glucose co-transporter 2 inhibitor
<i>Common adverse effects:</i>	Urinary tract infections, female genital mycotic infections
<i>Dosage form & strength:</i>	Tablet; 10 mg, 25 mg
<i>Product labeling:</i>	http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Jardiance/jardiance.pdf
Idelalisib – Zydelig (Gilead Sciences)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of patients with: Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least 2 prior systemic therapies. Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies.

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Table 1. New drugs approved by the US Food and Drug Administration (FDA): July 15, 2014 through August 15, 2014 (CONT.)

Idelalisib – Zydelig (Gilead Sciences)	
<i>Mechanism of action:</i>	Kinase inhibitor; induces apoptosis and inhibited proliferation in cell lines derived from malignant B-cells and in primary tumor cells
<i>Common adverse effects:</i>	Diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash
<i>Dosage form & strength:</i>	Tablets; 100 mg and 150 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205858lbl.pdf
Methotrexate – Rasuvo (Medac Pharma)	
<i>Comparative agents:</i>	Methotrexate
<i>Indication:</i>	Management of patients with severe, active rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, who are intolerant of or had an inadequate response to first-line therapy; symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy
<i>Mechanism of action:</i>	Folate metabolic inhibitor
<i>Common adverse effects:</i>	Nausea, abdominal pain, dyspepsia, stomatitis/mouth sores, rash, nasopharyngitis, diarrhea, liver function test abnormalities, vomiting, headache, bronchitis, thrombocytopenia, alopecia, leukopenia, pancytopenia, dizziness, photosensitivity, and “burning of skin lesion”
<i>Dosage form & strength:</i>	Injection, subcutaneous; manually triggered auto-injector; 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, and 30 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo
Olodaterol – Striverdi Respimat (Boehringer Ingelheim)	
<i>Comparative agents:</i>	Formoterol, salmeterol
<i>Indication:</i>	Treatment of patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema that are experiencing airflow obstruction
<i>Mechanism of action:</i>	Beta-2 adrenergic agonist
<i>Common adverse effects:</i>	Nasopharyngitis, upper respiratory tract infection, bronchitis, urinary tract infection, cough, dizziness, rash, diarrhea, back pain, and arthralgia
<i>Dosage form & strength:</i>	Multidose inhaler; 2.5 mcg/actuation
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203108s000lbl.pdf
Oxycodone hydrochloride / naloxone hydrochloride – Targiniq ER (Purdue Frederick)	
<i>Comparative agents:</i>	Oxycodone extended-release
<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/opioid antagonist (abuse deterrent)
<i>Common adverse effects:</i>	Nausea and vomiting
<i>Dosage form & strength:</i>	Extended-release tablets; 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205777lbl.pdf

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Table 1. New drugs approved by the US Food and Drug Administration (FDA): July 15, 2014 through August 15, 2014 (CONT.)

Suvorexant – Belsomra (Merck)	
<i>Comparative agents:</i>	New therapeutic class of hypnotic
<i>Indication:</i>	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
<i>Mechanism of action:</i>	Orexin receptor antagonist
<i>Common adverse effects:</i>	Somnolence
<i>Dosage form & strength:</i>	Tablets; 5 mg, 10 mg, 15 mg, 20 mg
<i>Product labeling:</i>	http://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf

Table 2. New dosage forms and indications approved by the FDA: July 15, 2014 through August 15, 2014

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/ route of administration		
Buprenorphine	<i>Butrans</i> (Purdue Pharma)	New 7.5 mcg/hour transdermal system
Canagliflozin/metformin	<i>Invokamet</i> (Janssen Pharmaceuticals)	New fixed-dose combination for the treatment of adult patients with type 2 diabetes
Fluticasone propionate	<i>Flonase Allergy Relief</i> (GlaxoSmithKline)	Prescription to over-the-counter switch for temporary relief of the symptoms of hay fever or upper respiratory allergies; switch will occur in 2015
New indications		
Aflibercept	<i>Eylea</i> (Regeneron)	Treatment of diabetic macular edema
Alglucosidase alfa	<i>Lumizyme</i> (Genzyme)	Treatment of Pompe disease
Bevacizumab	<i>Avastin</i> (Genentech)	Treatment of persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan
Ibrutinib	<i>Imbruvica</i> (Pharmacyclics/Janssen Biotech)	Treat patients with chronic lymphocytic leukemia (CLL) who carry a deletion in chromosome 17 (17p deletion), which is associated with poor responses to standard treatment for CLL

Table 3. Agents pending FDA approval: July 15, 2014 through August 15, 2014

Generic name	Brand name (Company)	Indication and comments
Recommended for approval by an FDA advisory panel		
Immune globulin infusion 10% (human) with recombinant human hyaluronidase	<i>HyQvia</i> (Baxter International & Halozyme Therapeutics)	Blood Products Advisory Committee voted 15 to 1 for subcutaneous use in the treatment of patients with primary immunodeficiency.
Tiotropium	<i>Spiriva Respimat</i> (Boehringer Ingelheim Pharmaceuticals)	Pulmonary-Allergy Drug Advisory Committee voted 10 to 3 in favor of a new indication for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema and to reduce exacerbations in COPD patients.
Agents scheduled for review by an FDA advisory panel		
Testosterone replacement therapy	Various	Review of adverse cardiovascular outcomes associated with the use of testosterone replacement therapy

Table 4. New drug / biologics license applications filed by manufacturer: July 15, 2014 through August 15, 2014

Generic name Brand name (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Brexipiprazole (Otsuka/Lundbeck)	Aripiprazole	Treatment of schizophrenia; adjunctive therapy for the treatment of major depressive disorder	Partial agonist of the dopamine D2 receptor; serotonin (5HT1A) receptor agonist	Akathisia, restlessness, insomnia, weight gain, nasopharyngitis	Oral	Brexipiprazole is also being evaluated for the treatment of agitation in Alzheimer's dementia.

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

Generic name Brand name (Company)	Warning
Ado-trastuzumab emtansine <i>Kadcyla</i> for injection (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hepatotoxicity</p> <ul style="list-style-type: none"> ...In clinical trials... one of which was fatal... nodular regenerative hyperplasia (NRH) should be considered ... and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver... <p>Hemorrhage</p> <ul style="list-style-type: none"> Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with <i>Kadcyla</i>. Some of these bleeding events resulted in fatal outcomes. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Hemorrhage <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409252.htm</p>

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Table 5. 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>Laboratory Tests</p> <ul style="list-style-type: none"> Refer to the prescribing information for peginterferon alfa and ribavirin for pretreatment, on-treatment, and posttreatment laboratory testing recommendations including hematology, biochemistry (including hepatic function tests), and pregnancy testing requirements. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303600.htm</p>
Calcitonin-salmon (rDNA origin) <i>Fortical</i> nasal spray (Upsher-Smith Laboratories)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypocalcemia</p> <ul style="list-style-type: none"> Hypocalcemia associated with tetany (ie, muscle cramps, twitching) and seizure activity has been reported with calcitonin therapy. Hypocalcemia must be corrected before initiating therapy with <i>Fortical</i> nasal spray. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with <i>Fortical</i> nasal spray. Use of <i>Fortical</i> nasal spray is recommended in conjunction with an adequate intake of calcium and vitamin D. <p>Malignancy</p> <ul style="list-style-type: none"> In a meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon (nasal spray or investigational oral formulations), the overall incidence of malignancies reported was higher among calcitonin-salmon–treated patients (4.1%) compared with placebo-treated patients (2.9%). This suggests an increased risk of malignancies in calcitonin-salmon–treated patients compared to placebo-treated patients. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> Hypocalcemia Malignancy <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409251.htm</p>
Class labeling change: Drugs to treat major depressive disorder (eg, antidepressants)	<p>WARNINGS AND PRECAUTIONS</p> <p>Angle-Closure Glaucoma</p> <ul style="list-style-type: none"> Angle-Closure Glaucoma: The pupillary dilation that occurs following the use of many antidepressant drugs may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. <p>Information for Patients</p> <ul style="list-style-type: none"> Patients should be advised that taking <DRUG NAME> can cause mild pupillary dilation, which in susceptible individuals can lead to an episode of angle-closure glaucoma. Preexisting glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure and have a prophylactic procedure (eg, iridectomy), if they are susceptible. <p>ADVERSE REACTIONS</p> <ul style="list-style-type: none"> ...angle-closure glaucoma <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409855.htm</p>
Class labeling change: Injectable corticosteroids	<p>WARNINGS</p> <p>Serious Neurologic Adverse Reactions with Epidural Administration</p> <ul style="list-style-type: none"> Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409825.htm</p>

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

Generic name Brand name (Company)	Warning
Class labeling changes: Testosterone-containing products	<p>WARNINGS</p> <ul style="list-style-type: none"> There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as <i>Delatestryl/AndroGel/Axiron/Aveed/Fortesta</i>. Evaluate patients who report symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with <i>Delatestryl/AndroGel/Axiron/Aveed/Fortesta</i> and initiate appropriate workup and management. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Vascular disorders – venous thromboembolism <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm402877.htm</p>
Clindamycin phosphate (injection) & HCL (capsules) <i>Cleocin</i> (Pfizer)	<p>WARNINGS</p> <p>Severe Skin Reactions</p> <ul style="list-style-type: none"> Severe skin reactions such as toxic epidermal necrolysis, some with fatal outcome, have been reported. In case of such an event, treatment should be permanently discontinued. <p>Benzyl Alcohol Toxicity in Pediatric Patients (“Gasping Syndrome”)</p> <ul style="list-style-type: none"> This product contains benzyl alcohol as a preservative. The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome,” and death in pediatric patients. <p>PRECAUTIONS</p> <p>Pregnancy</p> <ul style="list-style-type: none"> In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. Clindamycin should be used during the first trimester of pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. <i>Cleocin</i> phosphate sterile solution contains benzyl alcohol. Benzyl alcohol can cross the placenta. <p>ADVERSE REACTIONS</p> <p>Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Severe skin reactions such as toxic epidermal necrolysis, some with fatal outcome, have been reported. Cases of acute generalized exanthematous pustulosis (AGEP), erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. Anaphylactoid reactions have also been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. <p>Immune system</p> <ul style="list-style-type: none"> Drug reaction with eosinophilia and systemic symptoms (DRESS) cases have been reported. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm403291.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194129.htm</p>

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

Generic name Brand name (Company)	Warning
Denosumab <i>Prolia</i> (Amgen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hypocalcemia and Mineral Metabolism</p> <ul style="list-style-type: none"> Hypocalcemia following <i>Prolia</i> administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. These patients may also develop marked elevations of serum parathyroid hormone (PTH). <p>Musculoskeletal Pain</p> <ul style="list-style-type: none"> In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking <i>Prolia</i>. The time to onset of symptoms varied from one day to several months after starting <i>Prolia</i>. Consider discontinuing use if severe symptoms develop. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Parathyroid hormone (PTH): Marked elevation in serum PTH in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm307218.htm</p>
Denosumab <i>Xgeva</i> (Amgen)	<p>WARNINGS AND PRECAUTIONS</p> <p>An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm343116.htm</p>
Docetaxel (Hospira)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hematologic Effects</p> <ul style="list-style-type: none"> In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection. <p>Eye Disorders</p> <ul style="list-style-type: none"> Cystoid macular edema (CME) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered. <p>Alcohol Content</p> <ul style="list-style-type: none"> Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of docetaxel injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in docetaxel injection on the ability to drive or use machines immediately after the infusion. <p>Postmarketing Experiences</p> <ul style="list-style-type: none"> Respiratory: ...pneumonitis,...interstitial lung disease.... respiratory failure and pulmonary fibrosis.... may be associated with fatal outcome... Metabolism and Nutrition Disorders - Cases of hyponatremia have been reported. <p>USE IN SPECIFIC POPULATIONS</p> <p>Pediatric Use: Entire section updated</p> <p>Geriatric Use: Sections added for “Gastric Cancer” and “Head and Neck Cancer”</p> <p>Hepatic Impairment</p> <ul style="list-style-type: none"> ...The alcohol content of docetaxel injection should be taken into account when given to patients with hepatic impairment. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm396551.htm</p>

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

Generic name Brand name (Company)	Warning
Emtricitabine, rilpivirine, tenofovir disoproxil fumarate <i>Complera</i> (Gilead Sciences)	<p>WARNINGS AND PRECAUTIONS</p> <p>Coadministration with Other Products</p> <ul style="list-style-type: none"> • <i>Complera</i> should not be administered with rilpivirine (<i>Edurant</i>) unless needed for dose adjustment (eg, with rifabutin). <p>Drugs with No Observed or Predicted Interactions with <i>Complera</i></p> <ul style="list-style-type: none"> • ...No clinically significant drug interactions... Rilpivirine did not have a clinically significant effect on the pharmacokinetics of digoxin or metformin... <p>PATIENT COUNSELING INFORMATION</p> <ul style="list-style-type: none"> • For patients receiving rifabutin, an additional 25 mg tablet of rilpivirine (<i>Edurant</i>) once per day is recommended to be taken concomitantly with <i>Complera</i> and with a meal for the duration of rifabutin coadministration. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm318602.htm</p>
Everolimus <i>Afinitor</i> tablets & tablets for oral suspension (Novartis Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Noninfectious Pneumonitis</p> <ul style="list-style-type: none"> • Opportunistic infections such as <i>Pneumocystis jiroveci</i> pneumonia should be considered in the differential diagnosis. For patients who require use of corticosteroids for treatment of noninfectious pneumonitis, prophylaxis for <i>P. jiroveci</i> pneumonia may be considered. <p>Infections</p> <ul style="list-style-type: none"> • Localized and systemic infections, including... or <i>P. jiroveci</i> pneumonia • <i>P. jiroveci</i> pneumonia, some with a fatal outcome, has been reported in patients who received everolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for <i>P. jiroveci</i> pneumonia should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> • The following adverse reactions ... cholecystitis, cholelithiasis, arterial thrombotic events and reflex sympathetic dystrophy <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258494.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409257.htm</p>
Fondaparinux sodium <i>Arixtra</i> (Aspen)	<p>BOXED WARNING</p> <ul style="list-style-type: none"> • Optimal timing between the administration of <i>Arixtra</i> and neuraxial procedures is not known. <p>WARNINGS AND PRECAUTIONS</p> <p>Neuraxial Anesthesia and Postoperative Indwelling Epidural Catheter Use</p> <ul style="list-style-type: none"> • Optimal timing between the administration of <i>Arixtra</i> and neuraxial procedures is not known. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208639.htm</p>
Histrelin acetate <i>Vantas implant</i> (Endo Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Effect on QT/QTc Interval</p> <ul style="list-style-type: none"> • Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm242305.htm</p>

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

Generic name Brand name (Company)	Warning
Irbesartan / hydrochlorothiazide <i>Avalide</i> (Sanofi)	<p>WARNINGS AND PRECAUTIONS</p> <p>Lithium Interaction – Hydrochlorothiazide (drug interaction deleted)</p> <ul style="list-style-type: none"> Lithium generally should not be given with thiazides. <p>DRUG INTERACTIONS</p> <p>Irbesartan</p> <ul style="list-style-type: none"> No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine. Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan or thiazide diuretics. Monitor lithium levels in patients receiving <i>Avapro</i> and lithium. <p>Dual Blockade of the Renin-Angiotensin System (RAS)</p> <ul style="list-style-type: none"> In most patients no benefit has been associated with using 2 RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295999.htm</p>
Itraconazole capsules & solution <i>Sporanox</i> (Janssen Pharmaceuticals)	<p>BOXED WARNING</p> <p>Congestive Heart Failure, Cardiac Effects, and Drug Interactions</p> <ul style="list-style-type: none"> If signs or symptoms of congestive heart failure occur during administration of <i>Sporanox</i> (itraconazole) oral solution, continued <i>Sporanox</i> use should be reassessed. <p>Drug Interactions</p> <ul style="list-style-type: none"> Coadministration of the following drugs are contraindicated with <i>Sporanox</i> oral solution: methadone, disopyramide, dofetilide, dronedarone, quinidine, ergot alkaloids (such as dihydroergotamine, ergometrine [ergonovine], ergotamine, methylergometrine [methylergonovine]), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ranolazine, eplerenone, cisapride, lovastatin, simvastatin and, in subjects with renal or hepatic impairment, colchicine. Coadministration with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. <p>DRUG INTERACTIONS</p> <ul style="list-style-type: none"> Coadministration of a number of CYP3A4 substrates are contraindicated with <i>Sporanox</i>. Plasma concentrations increase for the following drugs: methadone, disopyramide, dofetilide, dronedarone, quinidine, ergot alkaloids (such as dihydroergotamine, ergometrine [ergonovine], ergotamine, methylergometrine [methylergonovine]), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ranolazine, eplerenone, cisapride, lovastatin, simvastatin and, in subjects with renal or hepatic impairment, colchicine. This increase in drug concentrations caused by coadministration with itraconazole may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Specific examples are listed in PRECAUTIONS: Drug Interactions.

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

Generic name Brand name (Company)	Warning
	<p>WARNINGS</p> <p>Interaction potential</p> <ul style="list-style-type: none"> <i>Sporanox</i> has a potential for clinically important drug interactions. Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in PRECAUTIONS: Drug Interactions. <p>Interchangeability</p> <ul style="list-style-type: none"> <i>Sporanox</i> (itraconazole) oral solution and <i>Sporanox</i> capsules should not be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. Only <i>Sporanox</i> oral solution has been demonstrated effective for oral and/or esophageal candidiasis. <p>Hydroxypropyl-β-cyclodextrin</p> <ul style="list-style-type: none"> <i>Sporanox</i> oral solution contains the excipient hydroxypropyl-β-cyclodextrin which produced adenocarcinomas in the large intestine and exocrine pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these adenocarcinomas is unknown. <p>PRECAUTIONS</p> <p>Information for Patients</p> <ul style="list-style-type: none"> <i>Sporanox</i> oral solution contains ...adenocarcinomas in the large intestine and exocrine ... The clinical relevance of these adenocarcinomas is unknown. Instruct patients that dizziness or blurred/double vision can sometimes occur with itraconazole. Advise patients that if they experience these events, they should not drive or use machines. <p>Drug Interactions: (Entire Section rewritten and enhanced table)</p> <p>Pregnancy: Teratogenic effects. Pregnancy Category C</p> <ul style="list-style-type: none"> <i>Sporanox</i> oral solution contains the excipient hydroxypropyl-β-cyclodextrin (HP-β-CD). HP-β-CD has no direct embryotoxic and no teratogenic effect... <p>Renal Impairment</p> <ul style="list-style-type: none"> ... The exposure of itraconazole may be lower in some patients with renal impairment. Caution should be exercised...and dose adjustment may be needed. <p>Hepatic Impairment</p> <ul style="list-style-type: none"> ... It is recommended that patients with impaired hepatic function be carefully monitored when taking <i>Sporanox</i>. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with <i>Sporanox</i> is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with preexisting hepatic function abnormalities or those who have experienced liver toxicity with other medications. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303524.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm403762.htm</p>

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

Generic name Brand name (Company)	Warning
Leuprolide acetate <i>Lupron</i> depot (Abbott Laboratories)	<p>WARNINGS AND PRECAUTIONS</p> <p>Effect on QT/QTc Interval</p> <ul style="list-style-type: none"> Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes. <p>ADVERSE REACTIONS</p> <p>Changes in Bone Density</p> <ul style="list-style-type: none"> Table 4 is revised to add the 95% confidence intervals (CIs) for the mean percent change from baseline in bone mineral density of lumbar spine in women treated with <i>Lupron</i> alone or <i>Lupron</i> plus norethindrone acetate. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262554.htm</p>
Linacotide <i>Linzess</i> (Forest Pharmaceuticals)	<p>BOXED WARNING</p> <p>WARNING: PEDIATRIC RISK</p> <ul style="list-style-type: none"> <i>Linzess</i> is contraindicated ... in nonclinical studies, administration of a single, clinically relevant adult oral dose of linacotide caused deaths due to dehydration in young juvenile mice. ...The safety and efficacy of <i>Linzess</i> has not been established in pediatric patients under 18 years of age <p>CONTRAINDICATIONS</p> <p><i>Linzess</i> is contraindicated in:</p> <ul style="list-style-type: none"> Pediatric patients under 6 years of age <p>WARNINGS AND PRECAUTIONS</p> <p>Pediatric Risk</p> <ul style="list-style-type: none"> <i>Linzess</i> is contraindicated in children under 6 years of age. The safety and effectiveness of <i>Linzess</i> in pediatric patients under 18 years of age have not been established. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop significant diarrhea and its potentially serious consequences <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409253.htm</p>
Obinutuzumab <i>Gazyva</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Thrombocytopenia</p> <ul style="list-style-type: none"> Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of <i>Gazyva</i> and chlorambucil or dose reductions of chlorambucil. Transfusion of blood products (ir, platelet transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm404996.htm</p>
Oxcarbazepine tablets & suspension <i>Trileptal</i> (Novartis Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity</p> <ul style="list-style-type: none"> DRESS, also known as multi-organ hypersensitivity, has occurred with <i>Trileptal</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342622.htm</p>

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

Generic name Brand name (Company)	Warning
Pramlintide acetate <i>Symlin</i> (AstraZeneca)	<p>WARNINGS AND PRECAUTIONS</p> <p>Patient Selection</p> <ul style="list-style-type: none"> • Proper patient selection is critical to the safe and effective use of <i>Symlin</i>. Before initiating <i>Symlin</i>, the patient’s HbA1c, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight should be reviewed. <i>Symlin</i> therapy should only be considered in patients with type 1 diabetes or patients with type 2 diabetes using mealtime insulin who fulfill the following criteria... <p>Hypoglycemia</p> <ul style="list-style-type: none"> • <i>Symlin</i> alone does not cause hypoglycemia. However, <i>Symlin</i> is indicated to be coadministered with mealtime insulin therapy, and in this setting there is an increased risk of severe hypoglycemia, particularly in patients with type 1 diabetes. If severe hypoglycemia associated with <i>Symlin</i> occurs, it is usually seen within the first 2 to 3 hours following a <i>Symlin</i> injection. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm123372.htm</p>
Ruxolitinib <i>Jakafi</i> (Incyte Corporation)	<p>WARNINGS AND PRECAUTIONS</p> <p>Risk of Infection</p> <p>Tuberculosis</p> <ul style="list-style-type: none"> • Tuberculosis infection has been reported in patients receiving <i>Jakafi</i>. <p>Myelofibrosis Symptom Exacerbation Following Interruption or Discontinuation of Treatment with <i>Jakafi</i></p> <ul style="list-style-type: none"> • Following discontinuation of <i>Jakafi</i>, symptoms of myelofibrosis generally return to pre-treatment levels over a period of approximately 1 week. Some patients have experienced 1 or more of the following adverse events after discontinuing <i>Jakafi</i>: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of <i>Jakafi</i>, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of <i>Jakafi</i>. Instruct patients not to interrupt or discontinue <i>Jakafi</i> therapy without consulting their physician. When discontinuing or interrupting therapy with <i>Jakafi</i> for reasons other than thrombocytopenia or neutropenia consider tapering the dose of <i>Jakafi</i> gradually rather than discontinuing abruptly. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377314.htm</p>
Somatropin (rDNA origin) <i>Humatrope</i> for injection (Eli Lilly and Company)	<p>WARNINGS AND PRECAUTIONS</p> <p>Neoplasms</p> <ul style="list-style-type: none"> • In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GH deficiency and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the more common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms. Monitor patients receiving somatropin therapy carefully for increased growth, or potential malignant changes, of preexisting nevi. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm223890.htm</p>

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

Generic name Brand name (Company)	Warning
Somatropin (rDNA origin) <i>Nutropin</i> AQ for injection (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Neoplasms</p> <ul style="list-style-type: none"> • In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the more common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence. • Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor. • Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms. • Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes, of preexisting nevi. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm402880.htm</p>
Sumatriptan <i>Alsuma</i> (Pfizer)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • The maximum recommended dose that may be given in 24 hours is 2 doses of <i>Alsuma</i> separated by at least 1 hour. <p>WARNINGS AND PRECAUTIONS</p> <p>Medication Overuse Headache</p> <ul style="list-style-type: none"> • Overuse of acute migraine drugs (eg, ergotamine, triptans, opioids, or combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). • Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache), may be necessary. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm403250.htm</p>
Sunitinib malate <i>Sutent</i> (Pfizer)	<p>WARNINGS AND PRECAUTIONS</p> <p>Proteinuria</p> <ul style="list-style-type: none"> • Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt <i>Sutent</i> and dose reduce for 24-hour urine protein ≥ 3 grams. Discontinue <i>Sutent</i> for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 grams despite dose reductions. The safety of continued <i>Sutent</i> treatment in patients with moderate to severe proteinuria has not been systematically evaluated. <p>Dermatologic Toxicities</p> <ul style="list-style-type: none"> • Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (eg, progressive skin rash often with blisters or mucosal lesions) are present, <i>Sutent</i> treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, <i>Sutent</i> treatment must not be re-started. • Necrotizing fasciitis, including fatal cases, has been reported in patients treated with <i>Sutent</i>, including of the perineum and secondary to fistula formation. Discontinue <i>Sutent</i> in patients who develop necrotizing fasciitis. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm224050.htm</p>

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

Generic name Brand name (Company)	Warning
Tamsulosin hydrochloride <i>Flomax</i> (Boehringer Ingelheim Pharmaceuticals)	<p>WARNINGS AND PRECAUTIONS</p> <p>Intraoperative Floppy Iris Syndrome</p> <ul style="list-style-type: none"> Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract and glaucoma surgery in some patients on or previously treated with alpha1 blockers, including <i>Flomax</i> capsules. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> Erythema multiforme, dermatitis exfoliative, visual impairment, and epistaxis During cataract and glaucoma surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha-1 blocker therapy. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm197087.htm</p>
Thalidomide <i>Thalomid</i> (Celgene Corporation)	<p>WARNINGS AND PRECAUTIONS</p> <p>Venous and Arterial Thromboembolism</p> <ul style="list-style-type: none"> The use of <i>Thalomid</i> in patients with multiple myeloma (MM) results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. Ischemic heart disease (11.1%), including myocardial infarction (1.3%), and stroke (cerebrovascular accident, 2.6%) have also occurred in patients with previously untreated MM treated with <i>Thalomid</i> and dexamethasone compared to placebo and dexamethasone (4.7%, 1.7%, and 0.9%, respectively) in 1 clinical trial. Consider thromboprophylaxis based on an assessment of individual patients’ underlying risk factors. Patients and physicians should be observant for the signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Agents that also may increase the risk of thromboembolism should be used with caution in patients receiving <i>Thalomid</i>. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm402899.htm</p>
Trastuzumab <i>Herceptin</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Cardiomyopathy</p> <ul style="list-style-type: none"> In Study 3 (1-year <i>Herceptin</i> treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%. <p>ADVERSE REACTION</p> <p>Clinical Trials Experience</p> <ul style="list-style-type: none"> In Study 3, a comparison of 3-weekly <i>Herceptin</i> treatment for 2 years 277 versus 1 year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year <i>Herceptin</i> treatment arm (8.1% vs 4.6% in the 1-year <i>Herceptin</i> treatment arm). More patients experienced at least 1 adverse reaction of grade 3 or higher in the 2-year <i>Herceptin</i> treatment arm (20.4%) compared with the 1-year <i>Herceptin</i> treatment arm (16.3%). The safety data from Studies 1 and 2 were obtained from 3,655 patients, of whom 2,000 received <i>Herceptin</i>; the median treatment duration was 51 weeks. The median age was 49 years (range, 24-80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392225.htm</p>

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

Triptorelin pamoate <i>Trelstar</i> (Actavis)	WARNINGS AND PRECAUTIONS Effect on QT/QTc Interval <ul style="list-style-type: none"> • Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm347049.htm
Ulipristal acetate <i>Ella</i> (Afaxys)	WARNINGS AND PRECAUTIONS CYP3A4 Inducers <ul style="list-style-type: none"> • A CYP3A4 inducer, rifampin, decreases the plasma concentration of <i>Ella</i> significantly. <i>Ella</i> should not be administered with CYP3A4 inducers USE IN SPECIFIC POPULATIONS: NURSING MOTHERS <ul style="list-style-type: none"> • Small quantities of ulipristal has been detected in human milk. The effect of this exposure on newborns/infants has not been studied; therefore, risk to the breastfed child cannot be excluded. Therefore, use of <i>Ella</i> by breastfeeding women is not recommended. http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm306971.htm

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