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): May 18, 2013 through July 17, 2013

Afatinib – Gilotrif (Boehringer Ingelheim)	
<i>Comparative agents:</i>	Erlotinib
<i>Indication:</i>	First-line treatment of patients with metastatic non-small-cell lung cancer whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test
<i>Mechanism of action:</i>	Binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling
<i>Common adverse effects:</i>	Diarrhea, rash/dermatitis, acneiform, stomatitis, paronychia, dry skin, decreased appetite, pruritus
<i>Dosage form & strength:</i>	Tablet; 20, 30, and 40 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201292s000lbl.pdf
Dabrafenib – TAFINLAR (GlaxoSmithKline)	
<i>Comparative agents:</i>	Trametinib
<i>Indication:</i>	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation
<i>Mechanism of action:</i>	Inhibitor of some mutated forms of BRAF kinases (eg, V600E, V600K, V600D enzymes), wild-type BRAF and CRAF kinases, and other kinases such as SIK1, NEK11, and LIMK1
<i>Common adverse effects:</i>	Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome
<i>Dosage form & strength:</i>	Capsule; 50 mg, 75 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202806s000lbl.pdf
Paroxetine – Brisdelle (Noven Therapeutics)	
<i>Comparative agents:</i>	Paroxetine
<i>Indication:</i>	Reduction of moderate to severe hot flashes associated with menopause
<i>Mechanism of action:</i>	Unknown; selective serotonin reuptake inhibitor
<i>Common adverse effects:</i>	Headache, fatigue, nausea, vomiting
<i>Dosage form & strength:</i>	Capsule; 7.5 mg
<i>Product labeling:</i>	http://www.brisdelle.com/pdf/PI_MedGuide.pdf

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Table 1. New drugs approved by the US Food and Drug Administration (FDA): May 18, 2013 through July 17, 2013 (CONT.)

Recombinant coagulation factor IX – <i>Rixubis</i> (Baxter Healthcare)	
<i>Comparative agents:</i>	Coagulation factor IX
<i>Indication:</i>	Use in patients with hemophilia B who are 16 years of age and older for the control and prevention of bleeding episodes, perioperative management, and routine use to prevent or reduce the frequency of bleeding episodes.
<i>Mechanism of action:</i>	Replacement of missing coagulation factor
<i>Common adverse effects:</i>	Dysgeusia, pain in extremity, and positive test for furin antibody
<i>Dosage form & strength:</i>	Injection; 250, 500, 1000, 2000, and 3000 IU
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM358875.pdf
Trametinib – <i>MEKINIST</i> (GlaxoSmithKline)	
<i>Comparative agents:</i>	Dabrafenib
<i>Indication:</i>	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation
<i>Mechanism of action:</i>	Reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2.
<i>Common adverse effects:</i>	Rash, diarrhea, and lymphedema
<i>Dosage form & strength:</i>	Tablet; 0.5 mg, 1 mg, and 2 mg
<i>Product labeling:</i>	http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204114s000lbl.pdf

Table 2. New dosage forms and indications approved by the FDA: May 18, 2013 through July 17, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/route of administration		
Buprenorphine-naloxone	<i>Zubsolv</i> (Orexo)	Sublingual tablet formulation used for maintenance treatment for opioid dependence in combination with a treatment plan that includes counseling and psychological support
New indications		
Denosumab	<i>Xgeva</i> (Amgen)	Treatment of giant cell tumor of the bone
Lenalidomide	<i>Revlimid</i> (Celgene Corporation)	Treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after 2 prior therapies that have included bortezomib
Lurasidone	<i>Latuda</i> (Sunovion Pharmaceuticals)	Mono- and adjunctive therapy in adult patients with bipolar depression
Micafungin sodium	<i>Mycamine</i> (Astellas Pharma)	Treatment of pediatric patients 4 months and older with candidemia, acute disseminated candidiasis, <i>Candida</i> peritonitis and abscesses, esophageal candidiasis, and prophylaxis of <i>Candida</i> infections in patients undergoing hematopoietic stem cell transplant
Rivastigmine transdermal system	<i>Exelon</i> patch (Novartis)	Now approved for all stages of Alzheimer's disease
Telavancin	<i>Vibativ</i> (Theravance Inc.)	Treatment of patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by <i>Staphylococcus aureus</i> . It should be used for the treatment of HABP/VABP only when alternative treatments are not suitable.

Table 3. Agents pending FDA approval: May 18, 2013 through July 17, 2013

Generic name	Brand name (Company)	Indication and comments
Complete response letter: More information required		
Suvorexant	(Merck)	Approved based on the use of a lower dose (10 mg, 15 mg, and 20 mg) not the requested higher doses (up to 40 mg). Manufacturing data of a new 10 mg dosage form will be required. The negative complete response letter follows a positive advisory committee vote despite questions raised by the scientist from the FDA regarding the drug's safety (eg, daytime drowsiness, driving difficulties) at the suggested dose.
Testosterone undecanoate injection	AVEED (Endo Pharmaceuticals)	Treatment of hypogonadism. No additional clinical information was requested, instead it appears the response is related to the required REMS program.
Tivozanib	(Aveo Pharmaceuticals)	Treatment of advanced renal cell carcinoma
Complete response letter: Nonapproval		
Gabapentin	Sefelsa (Depomed)	Twice-daily formulation for the treatment of menopausal vasomotor symptoms
Rivaroxaban	Xarelto (Janssen Pharmaceuticals)	Reduces the risk of stent thrombosis in patients with acute coronary syndrome
Delayed decision by the FDA		
Elosulfase alfa	Vimizim (BioMarin Pharmaceutical)	Treatment of patients suffering from mucopolysaccharidosis type IVA (MPS IVA) or morquio A syndrome. Priority review, but the date on which the agency will announce drug approval status was delayed by 3 months at the end of May 2013.
Recommended for nonapproval by an FDA advisory panel		
Efinaconazole	(Valeant Pharmaceuticals)	Treatment of onychomycosis; delayed based on questions related to the container closure apparatus and not the drug's safety or efficacy
Agents scheduled for Review by an FDA advisory panel		
Morphine sulfate / oxycodone hydrochloride	MOXDUO (QRxPharma)	Management of moderate to severe acute pain where the use of an opioid analgesic is appropriate
Sugammadex sodium	(Organon)	Routine reversal of moderate and deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium and immediate reversal of NMB at 3 minutes after administration of rocuronium

Table 4. New drug/biologics license applications filed by manufacturer: May 18, 2013 through July 17, 2013

Generic name <i>Brand name</i> (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Peginterferon beta-1a <i>Plegridy</i> (Biogen Idec)	Interferon beta-1a	Treatment of relapsing forms of multiple sclerosis	Unknown	Flu-like symptoms, injection site reactions	Injection; subcutaneous	
Ibrutinib	–	Treatment of relapsed/refractory chronic lymphocytic leukemia and relapsed/refractory mantle cell lymphoma	Bruton's tyrosine kinase (BTK) inhibitor	Diarrhea, fatigue, nausea, pneumonia, neutropenia, thrombocytopenia, anemia	Oral	Classified as "breakthrough therapy" by the FDA

Table 5. Supplemental applications filed by manufacturer: May 18, 2013 Through July 17, 2013

Generic name	<i>Brand name</i> (Company)	Comments
Dabrafenib and trametinib	(GlaxoSmithKline)	Used in combination to treat adult patients with unresectable or metastatic melanoma with a BRAF V600E or K mutation
Sorafenib	<i>Nexavar</i> (Bayer/Onyx)	Treatment of radioactive iodine-refractory differentiated thyroid cancer

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

Generic name Brand name (Company)	Warning
Adalimumab injection <i>Humira</i> (AbbVie Inc.)	<p>WARNINGS AND PRECAUTIONS</p> <p>Serious Infections</p> <ul style="list-style-type: none"> • Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving adalimumab, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (ie, disseminated) tuberculosis. • Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. <p>Malignancies: The potential risk with the combination of azathioprine or 6-mercaptopurine and adalimumab should be carefully considered.</p> <p>Hypersensitivity Reactions: Anaphylaxis and angioneurotic edema have been reported following adalimumab administration.</p> <p>Immunizations: It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization.</p> <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> • General disorders and administration site conditions: Pyrexia • Neoplasms benign, malignant, and unspecified (include cysts and polyps): Merkel cell carcinoma (neuroendocrine carcinoma of the skin) <p>DRUG INTERACTIONS</p> <p>Biologic Products: Concomitant administration of adalimumab with other biologic disease-modifying anti-rheumatic drugs (DMARDs; eg, anakinra and abatacept) or other tumor necrosis factor (TNF) blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.</p> <p>Use in Specific Populations</p> <p>Pregnancy: Pregnancy Category B: See product labeling for extensive changes to all subsections related to use during pregnancy.</p> <p>Nursing Mothers: Limited data from published literature indicate that adalimumab is present in low levels in human milk and is not likely to be absorbed by a breastfed infant.</p> <p>Pediatric Use: Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect immune response in the in utero exposed newborn and infant.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194134.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
All codeine-containing products (Various)	<p>BOXED WARNING</p> <p>WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6.</p> <p>CONTRAINDICATIONS</p> <p>Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.</p> <p>WARNINGS</p> <p>Codeine Phosphate</p> <ul style="list-style-type: none"> • Death Related to Ultra-Rapid Metabolism of Codeine to Morphine Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (ie, multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultrarapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). • Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for postoperative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy. • When prescribing codeine-containing drugs, health care providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose. <p>Pediatric Use</p> <ul style="list-style-type: none"> • Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultrarapid metabolizers of codeine (ie, multiple copies of the gene for CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for postoperative pain management in these patients. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm356221.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
Amphetamine salts, mixed (Various)	<p>WARNINGS AND PRECAUTIONS</p> <p>Peripheral Vasculopathy, including Raynaud’s phenomenon</p> <ul style="list-style-type: none"> Stimulants used to treat attention deficit hyperactivity disorder (ADHD) are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud’s phenomenon, were observed in postmarketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (eg, rheumatology referral) may be appropriate for certain patients. <p>PATIENT COUNSELING INFORMATION</p> <p>Circulation Problems in Fingers and Toes (peripheral vasculopathy, including Raynaud’s phenomenon)</p> <ul style="list-style-type: none"> Instruct patients about the risk of peripheral vasculopathy, including Raynaud’s phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes. Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360259.htm</p>
Colesevelam <i>Welchol</i> (Daiichi Sankyo)	<p>WARNINGS AND PRECAUTIONS</p> <p>Phenylketonurics: <i>Welchol</i> for oral suspension contains 13.5 mg phenylalanine per 1.875 g packet and 27 mg phenylalanine per 3.75 g packet.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360430.htm</p>
Cyclosporine products (Various)	<p>WARNINGS</p> <p>Kidney, Liver, and Heart Transplant/Nephrotoxicity</p> <ul style="list-style-type: none"> When considering the development of cyclosporine-associated nephropathy, it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating through concentrations of cyclosporine. This is particularly true during the first 6 posttransplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients are prolonged perfusion time, warm ischemia time, and episodes of acute toxicity and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined. Reversibility of arteriopathy has been reported after stopping cyclosporine or lowering the dosage. In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fails to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the cyclosporine dose to excessive blood concentrations. Due to the potential for additive or synergistic impairment of renal function, caution should be exercised when co-administering cyclosporine with other drugs that may impair renal function. Encephalopathy, including Posterior Reversible Encephalopathy Syndrome (PRES), has been described both in postmarketing reports and in the literature.

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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
	<p>Special Excipients</p> <p>Alcohol (ethanol) : The alcohol content of cyclosporine should be taken into account when given to patients in whom alcohol intake should be avoided or minimized, eg, pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients, or pediatric patients. For an adult weighing 70 kg, the maximum daily oral dose would deliver about 1 g of alcohol, which is approximately 6% of the amount of alcohol contained in a standard drink.</p> <p>PRECAUTIONS</p> <p>Drug Interactions</p> <p>Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety</p> <ul style="list-style-type: none"> • All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant use of nonsteroidal anti-inflammatory drugs with cyclosporine, particularly in the setting of dehydration, may potentiate renal dysfunction. Caution should be exercised when using other drugs that are known to impair renal function. <p>Drugs/Dietary Supplements that Decrease Cyclosporine Concentrations</p> <p>Three new subsections have been added after the table as follows:</p> <p>Bosentan /Boceprevir/Telaprevir: Coadministration of bosentan (250 - 1000 mg every 12 hours based on tolerability) and cyclosporine (300 mg every 12 hours for 2 days then dosing to achieve a C_{min} of 200-250 ng/mL) for 7 days</p> <p>Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents</p> <p>Ambrisentan: Coadministration of ambrisentan (5 mg daily) and cyclosporine (100-150 mg twice daily initially, then dosing to achieve C_{min} 150-200 ng/mL) for 8 days in healthy subjects resulted in mean increases in ambrisentan AUC and C_{max} of approximately 2-fold and 1.5-fold, respectively, compared to ambrisentan alone</p> <p>Anthracycline antibiotics: High doses of cyclosporine (eg, at starting intravenous dose of 16 mg/kg/day) may increase the exposure to anthracycline antibiotics (eg, doxorubicin, mitoxantrone, daunorubicin) in cancer patients.</p> <p>Bosentan: In healthy subjects, coadministration of bosentan and cyclosporine resulted in mean increases in dose-normalized bosentan trough concentrations on day 1 and day 8 of approximately 21-fold and 2-fold, respectively, compared to when bosentan was given alone as a single dose on day 1.</p> <p>Nifedipine: Frequent gingival hyperplasia when nifedipine is given concurrently with cyclosporine has been reported. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of cyclosporine.</p> <p>Pregnancy Category C: The alcohol content of the cyclosporine formulations should also be taken into account in pregnant women.</p> <p>Nursing Mothers: Cyclosporine is present in breast milk. Because of the potential for serious adverse drug reactions in nursing infants from cyclosporine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Cyclosporine contains ethanol. Ethanol will be present in human milk at levels similar to that found in maternal serum and if present in breast milk will be orally absorbed by a nursing infant.</p> <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience, Psoriasis: Cases of transformation to erythrodermic psoriasis or generalized pustular psoriasis upon either withdrawal or reduction of cyclosporine in patients with chronic plaque psoriasis have been reported.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319408.htm http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319403.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
Dexmethylphenidate products <i>Focalin & Focalin XR</i> (Novartis)	See entry for Amphetamine salts, mixed http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360009.htm
Dextroamphetamine products (Various)	See entry for Amphetamine salts, mixed http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm359954.htm
Emtricitabine/tenofovir disoproxil fumarate <i>Truvada</i> (Gilead)	WARNINGS AND PRECAUTIONS Coadministration with Other Products <ul style="list-style-type: none"> Do not coadminister <i>Truvada</i> with <i>Stribild</i> (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194544.htm
Eplerenone <i>Inspra</i> (Pfizer)	WARNINGS AND PRECAUTIONS Hyperkalemia: The risk of hyperkalemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB). DRUG INTERACTIONS ACE Inhibitors and Angiotensin II Receptor Antagonists: The risk of hyperkalemia may increase when eplerenone is used in combination with an ACE inhibitor and/or an ARB. A close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function, eg, the elderly. http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm119305.htm
Estradiol Transdermal System <i>Vivelle-Dot</i> (Novartis)	BOX WARNING Updated text to reflect the current recommended estrogen-class labeling CONTRAINDICATIONS <ul style="list-style-type: none"> Added: Known anaphylactic reaction or angioedema or hypersensitivity to <i>Vivelle-Dot</i> Added: Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders WARNINGS Added/changed subheadings and modified the accompanying text to reflect the current recommended estrogen-class labeling Malignant Neoplasm Ovarian Cancer: The WHI estrogen plus progestin substudy reported a statistically nonsignificant increased risk of ovarian cancer. Hereditary Angioedema: Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. PRECAUTIONS Updated to reflect current recommended estrogen-class labeling http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm356105.htm
Gemcitabine for injection <i>Gemzar</i> (Eli Lilly)	WARNINGS AND PRECAUTIONS Capillary Leak Syndrome: Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Discontinue gemcitabine if CLS develops during therapy. ADVERSE REACTIONS Postmarketing Experience <ul style="list-style-type: none"> Added: Vascular Disorders: Peripheral vasculitis, gangrene, and capillary leak syndrome http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm356107.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
Idursulfase <i>Elaprase</i> (Shire)	<p>BOXED WARNING</p> <p>Life-threatening anaphylactic reactions, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have occurred in some patients during and up to 24 hours after <i>Elaprase</i> infusions. Closely observe patients during and after <i>Elaprase</i> administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur.</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Hypersensitivity Reactions Including Anaphylaxis</p> <ul style="list-style-type: none"> • Serious hypersensitivity reactions, including anaphylaxis, have occurred during and up to 24 hours after infusion. Some of these reactions were life-threatening and included respiratory distress, hypoxia, hypotension, urticaria, and angioedema of the throat or tongue, regardless of duration of the course of treatment. • Medical management included treatment with antihistamines, inhaled beta-adrenergic agonists, corticosteroids, oxygen, and vasopressors. Treatment was discontinued for some patients, while others continued treatment with premedication and a slower infusion rate. <p>ADVERSE REACTIONS</p> <p><i>Entire section revised</i></p> <p>USE IN SPECIFIC POPULATIONS</p> <p>Nursing Mothers: <i>Elaprase</i> was excreted in breast milk of lactating rats at a concentration higher (4- to 5-fold) than that of the plasma. It is not known whether <i>Elaprase</i> is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when <i>Elaprase</i> is administered to a nursing woman.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360460.htm</p>
Immune globulin products (human) (Various)	<p>BOXED WARNING</p> <ul style="list-style-type: none"> • FDA has analyzed recent data that has strengthened the association between the use of intravenous, subcutaneous, and intramuscular human immune globulin products and the risk of thrombosis. Additional caution regarding the use of these products is warranted. • FDA is requiring manufacturers to add information on thrombosis to the current boxed warning in the labels of all intravenous human immune globulin products and to add a boxed warning to the labels of all subcutaneous and intramuscular human immune globulin products to highlight the risk of thrombosis and to add information on its mitigation. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360566.htm</p>
Ipilimumab <i>Yervoy</i> (Bristol-Myers Squibb)	<p>WARNINGS AND PRECAUTIONS</p> <p>Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations: Autoimmune central neuropathy (encephalitis), neurosensory hypoacusis, myositis, polymyositis, ocular myositis, and sarcoidosis</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm328023.htm</p>
Lapatinib <i>Tykerb</i> (SmithKline Beecham)	<p>WARNINGS AND PRECAUTIONS</p> <p>Diarrhea: Diarrhea has been reported during treatment with <i>Tykerb</i>. The diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs early during treatment with <i>Tykerb</i>, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4 to 5 days. Early identification and intervention is critical for the optimal management of diarrhea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhea with antidiarrheal agents (such as loperamide) after the first unformed stool is recommended. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, use of antibiotics such as fluoroquinolones (especially if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4 neutropenia), and interruption or discontinuation of therapy with <i>Tykerb</i>.</p> <p>PATIENT COUNSELING INFORMATION</p> <p>Information for Patients: <i>Tykerb</i> often causes diarrhea which may be severe in some cases. Patients should be told how to manage and/or prevent diarrhea and to inform their physician immediately if there is any change in bowel patterns or severe diarrhea occurs during treatment with <i>Tykerb</i>.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm121837.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
Linagliptin-containing products <i>Tradjenta</i> & <i>Jentadueto</i> (Boehringer Ingelheim)	<p>WARNINGS AND PRECAUTIONS</p> <p>Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using <i>Jentadueto</i>.</p> <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience: Acute pancreatitis, including fatal pancreatitis</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360497.htm</p>
Magnesium sulfate injectable products (Various)	<p>WARNINGS</p> <p>Fetal Harm: Continuous administration of magnesium sulfate beyond 5 to 7 days to pregnant women can cause fetal harm.</p> <p>PRECAUTIONS</p> <p>Pregnancy</p> <p>Teratogenic Effects: Pregnancy Category D</p> <p>Nonteratogenic Effects: When administered by continuous IV infusion (especially for more than 24 hours preceding delivery) to control convulsions in a toxemic woman, the newborn may show signs of magnesium toxicity, including neuromuscular or respiratory depression.</p> <p>Labor and Delivery: Administration of magnesium sulfate for the unapproved treatment of preterm labor should be performed by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm356090.htm</p>
Methylphenidate products (Various)	<p>See entry for Amphetamine salts, mixed</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360053.htm</p>
Natalizumab <i>Tysabri</i> (Biogen Idec)	<p>WARNINGS AND PRECAUTIONS</p> <p>Progressive Multifocal Leukoencephalopathy (PML): PML has been reported following drug discontinuation in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of natalizumab therapy.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm355780.htm</p>
Olmesartan (Various)	<p>Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan and sometimes require hospitalization. If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued.</p> <p>http://www.fda.gov/Drugs/DrugSafety/ucm359477.htm</p>
Perampanel <i>Fycompa</i> (EISAI)	<p>WARNINGS AND PRECAUTIONS</p> <p>Psychiatric and Behavioral Reactions: Homicidal ideation and/or threat were exhibited in 0.1% of 4,368 perampanel-treated patients in controlled and open-label studies, including nonepilepsy studies.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360437.htm</p>
Phentermine hydrochloride <i>Suprenza</i> (Citius Pharms)	<p>WARNINGS AND PRECAUTIONS</p> <p>Risk of Allergic Reactions due to Tartrazine: <i>Suprenza</i> 15 mg and 30 mg orally disintegrating tablet (ODT) contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360021.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
Plerixafor <i>Mozobil</i> (Genzyme Corporation)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> History of hypersensitivity to <i>Mozobil</i> Anaphylactic shock has occurred with use of <i>Mozobil</i>. <p>WARNINGS AND PRECAUTIONS</p> <p>Anaphylactic Shock and Hypersensitivity Reactions</p> <ul style="list-style-type: none"> Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening with clinically significant hypotension and shock, have occurred in patients receiving <i>Mozobil</i>. Observe patients for signs and symptoms of hypersensitivity during and after <i>Mozobil</i> administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer <i>Mozobil</i> when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. <p>ADVERSE REACTIONS</p> <p>Clinical Trials Experience: Hyperleukocytosis: In clinical trials, white blood cell counts of 100,000/mcL or greater were observed on the day prior to or any day of apheresis.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm359917.htm</p>
Rituximab injection <i>Rituxan</i> (Genentech)	<p>WARNINGS AND PRECAUTIONS</p> <p>Severe Mucocutaneous Reactions: Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. Discontinue rituximab in patients who experience a severe mucocutaneous reaction. The safety of re-administration of rituximab to patients with severe mucocutaneous reactions has not been determined.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm328041.htm</p>
Rivastigmine <i>Exelon</i> (Novartis)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Previous history of application site reactions with rivastigmine transdermal patch suggestive of allergic contact dermatitis. <p>WARNINGS AND PRECAUTIONS</p> <p>Skin Reactions</p> <ul style="list-style-type: none"> Skin application site reactions may occur with <i>Exelon</i> patch and are usually mild or moderate in intensity. These reactions are not in themselves an indication of sensitization. However, use of rivastigmine patch may lead to allergic contact dermatitis. Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (eg, increasing erythema, edema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued. In patients who develop application site reactions to <i>Exelon</i> patch suggestive of allergic contact dermatitis and who still require rivastigmine, treatment should be switched to oral rivastigmine only after negative allergy testing and under close medical supervision. It is possible that some patients sensitized to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form. There have been isolated postmarketing reports of patients experiencing disseminated hypersensitivity reactions of the skin when administered rivastigmine irrespective of the route of administration (oral or transdermal). In these cases, treatment should be discontinued. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience: Abnormal liver function tests, disseminated cutaneous hypersensitivity reactions</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360439.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
Saxagliptin & saxagliptin/metformin <i>Onglyza</i> & <i>Kombiglyze XR</i> (Bristol-Myers Squibb)	<p>CONTRAINDICATIONS Saxagliptin is contraindicated in patients with a history of a serious hypersensitivity reaction to saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions.</p> <p>ADVERSE REACTIONS Clinical Trials Experience Adverse Reactions with Monotherapy and with Add-On Combination Therapy: The 10 mg dosage is not an approved dosage. Hypoglycemia: In the add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for saxagliptin 5 mg and 6.3% for placebo. Confirmed hypoglycemia was reported in 1.6% of the saxagliptin-treated patients and in none of the placebo-treated patients</p> <p>USE IN SPECIFIC POPULATIONS Pediatric Use: Safety and effectiveness of saxagliptin in pediatric patients under 18 years of age have not been established.</p> <p>PATIENT COUNSELING INFORMATION See FDA-approved patient labeling (Medication Guide).</p> <ul style="list-style-type: none"> • Pancreatitis • Hypersensitivity Reactions • Missed Dose <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm283036.htm</p>
Spironolactone & spironolactone- containing products (Various)	<p>CONTRAINDICATIONS Addison’s disease or other conditions associated with hyperkalemia, and with concomitant use of eplerenone.</p> <p>WARNINGS Concomitant administration of <i>Aldactone</i> with the following drugs or potassium sources may lead to severe hyperkalemia: other potassium-sparing diuretics; ACE inhibitors; angiotensin II antagonists; aldosterone blockers; nonsteroidal anti-inflammatory drugs (NSAIDs), eg, indomethacin; heparin and low-molecular-weight heparin; other drugs known to cause hyperkalemia; potassium supplements; diet rich in potassium; salt substitutes containing potassium</p> <p>PRECAUTIONS</p> <ul style="list-style-type: none"> • Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined. • Angiotensin II antagonists, aldosterone blockers, heparin, low-molecular-weight heparin, and other drugs known to cause hyperkalemia: Concomitant administration may lead to severe hyperkalemia. • Cholestyramine: Hyperkalemic metabolic acidosis has been reported in patients given <i>Aldactone</i> concurrently with cholestyramine. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360045.htm</p>
Terbinafine <i>Lamisil</i> formulations (Novartis)	<p>WARNINGS AND PRECAUTIONS Serious Skin/Hypersensitivity Reactions: There have been postmarketing reports of serious skin/hypersensitivity reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome). Manifestations of DRESS syndrome may include cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more organ complications such as hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. If progressive skin rash or signs/symptoms of the above drug reactions occur, treatment with <i>Lamisil</i> tablets should be discontinued.</p> <p>ADVERSE REACTIONS Postmarketing Experience: Skin and subcutaneous tissue disorders: . . .drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360349.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
Tolcapone <i>Tasmar</i> (Valeant Pharmaceuticals)	<p>WARNINGS</p> <p>Patients Falling Asleep During Activities of Daily Living and Somnolence</p> <p>PRECAUTIONS</p> <p>Hallucinations/Psychotic-Like Behavior; Impulse Control/Compulsive Behaviors; Geriatric Use</p> <p>Patients older than 75 years of age may be more likely to develop hallucinations than patients younger than 75 years of age, while patients older than 75 may be less likely to develop dystonia.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm356111.htm</p>
Ursodiol <i>Urso & Urso Forte</i> (Aptalis Pharma)	<p>WARNINGS AND PRECAUTIONS</p> <p>Abnormal Liver Function Tests</p> <ul style="list-style-type: none"> • Liver function tests (γ-GT, alkaline phosphatase, AST, ALT) and bilirubin levels should be monitored every month for 3 months after start of therapy, and every 6 months thereafter. This monitoring will allow the early detection of a possible deterioration of the hepatic function. Treatment discontinuation should be considered if the above parameters increase to a level considered clinically significant in patients with stable historical liver function test levels. • Caution has to be exercised to maintain the bile flow of the patients taking ursodiol. <p>ADVERSE REACTIONS</p> <p>Postmarketing Experience</p> <ul style="list-style-type: none"> • Hepatobiliary disorders: jaundice (or aggravation of preexisting jaundice) • Abnormal laboratory tests: ALT increased, AST increased, blood alkaline phosphatase increased, blood bilirubin increased, γ-GT increased, hepatic enzyme increased, liver function test abnormal, transaminases increased <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360280.htm</p>
Valproic acid/ divalproex sodium products (Various)	<p>BOXED WARNING: Fetal Risk</p> <p>Valproate can cause major congenital malformations, particularly neural tube defects (eg, spina bifida). In addition, valproate can cause decreased IQ scores following in utero exposure. Valproate is therefore contraindicated in pregnant women treated for prophylaxis of migraine. Valproate should only be used to treat pregnant women with epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable.</p> <p>WARNINGS AND PRECAUTIONS</p> <p>Birth Defects: Valproate can cause fetal harm when administered to a pregnant woman. Pregnancy registry data show that maternal valproate use can cause neural tube defects and other structural abnormalities (eg, craniofacial defects, cardiovascular malformations and malformations involving various body systems). The rate of congenital malformations among babies born to mothers using valproate is about 4 times higher than the rate among babies born to epileptic mothers using other antiseizure monotherapies. Evidence suggests that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population.</p> <p>Decreased IQ Following in utero Exposure: Valproate can cause decreased IQ scores following in utero exposure.</p> <p>USE IN SPECIFIC POPULATIONS</p> <p>Pregnancy: Fetal risk summary: In animal studies, offspring with prenatal exposure to valproate had structural malformations similar to those seen in humans and demonstrated neurobehavioral deficits.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360487.htm</p>

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