Current FDA-Related Drug Information

Approvals, Submission, and Important Labeling Changes for US Marketed Pharmaceuticals

Danial E. Baker, PharmD, FASHP, FASCP*

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 bakerdan@wsu.edu.

Table 1. New drugs approved by the US Food and Drug Administration (FDA): March 16, 2013 through April 15, 2013

Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine) – (Cangene Corporation)	
<i>Comparative agents:</i>	Botulism Antitoxin Bivalent (Equine) Types A and B
<i>Indication:</i>	Treatment of symptomatic botulism
<i>Mechanism of action:</i>	Antitoxin
<i>Common adverse effects:</i>	Headache, nausea, and urticaria
<i>Dosage form & strength:</i>	Injection: Will be maintained in the Strategic National Stockpile and distributed through the Centers for Disease Control and Prevention Drug Service.
<i>Product labeling:</i>	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf
Canagliflozin – Invokana (Janssen Pharmaceuticals)	
<i>Comparative agents:</i>	None: first-in-class sodium-glucose co-transporter 2 (SGLT2) inhibitor
<i>Indication:</i>	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<i>Mechanism of action:</i>	SGLT2 inhibitor
<i>Common adverse effects:</i>	Female genital mycotic infections, urinary tract infection, increased urination
<i>Dosage form & strength:</i>	Tablets: 100 mg and 300 mg
<i>Product labeling:</i>	http://www.invokanahcp.com/prescribing-information.pdf

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*Director, Drug Information Center, College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495.

Table 1. New drugs approved by the US Food and Drug Administration (FDA): March 16, 2013 through April 15, 2013 (CONT.)

Dimethyl fumarate – Tecfidera (Biogen Idec)	
<i>Comparative agents:</i>	None
<i>Indication:</i>	Treatment of patients with relapsing forms of multiple sclerosis
<i>Mechanism of action:</i>	Unknown; activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which is involved in the cellular response to oxidative stress
<i>Common adverse effects:</i>	Flushing, abdominal pain, diarrhea, and nausea
<i>Dosage form & strength:</i>	Delayed-release capsules: 120 mg and 240 mg
<i>Product labeling:</i>	http://www.tecfidera.com/pdfs/full-prescribing-information.pdf
Doxylamine succinate / Pyridoxine HCl – Diclegis (Duchesnay)	
<i>Comparative agents:</i>	Individual ingredients
<i>Indication:</i>	Treatment of nausea and vomiting of pregnancy in woman who do not respond to conservative management, including dietary and lifestyle modifications
<i>Mechanism of action:</i>	Unknown
<i>Common adverse effects:</i>	Somnolence
<i>Dosage form & strength:</i>	Delayed-release tablet: 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride
<i>Product labeling:</i>	http://www.diclegis.com/pdf/Diclegis_Full_Prescribing_Information.pdf

Table 2. New dosage forms and indications approved by the FDA: March 16, 2013 through April 15, 2013

Generic name	Brand name (Company)	Indication and comments
New dosage forms/strength/ route of administration		
Levonorgestrel/ethinyl estradiol; ethinyl estradiol	<i>Quartette</i> (Teva)	Prevention of pregnancy; 91-day oral dosing regimen designed to prevent pregnancy and decrease the number of annual periods.
Rabeprazole sodium	<i>AcipHex</i> Sprinkle (Eisai)	Treatment of gastroesophageal reflux disease in children ages 1 year to 11 years
Tobramycin inhalation powder	<i>TOBI</i> Podhaler (Novartis)	Dry powder inhaler for the management of cystic fibrosis patients with <i>Pseudomonas aeruginosa</i>
New indications		
Carbinoxamine maleate	<i>Karbinal</i> ER (Tris Pharma)	Extended-release oral suspension (4 mg/5 mL) for the treatment of seasonal and perennial allergic rhinitis in children 2 and older

Table 3. Agents pending FDA approval: March 16, 2013 through April 15, 2013

Generic name	Brand name (Company)	Indication and comments
Complete response letter: more information required		
Hepatitis B vaccine	HEPLISAV (Dynavax)	Additional data on the safety of the product and concerns related to the “novel” adjuvant used in the formulation
Q-Pan H5N1 vaccine	(GlaxoSmithKline)	Used to prevent “bird flu”; safety concerns regarding the adjuvant used in the vaccine
Treprostinil diolamine	(United Therapeutics)	Oral agent for the treatment of pulmonary arterial hypertension
Delayed decision by the FDA		
Sugammadex sodium	(Merck)	Reversal of neuromuscular blockade in general anaesthesia; selective relaxant binding agent

Table 4. New drug / biologics license applications filed by manufacturer: March 16, 2013 through April 15, 2013

Generic name Brand name (Company)	Comparative agents	Indication	Mechanism of action	Common adverse effects	Dosage form or route	Comments
Omeprazole & aspirin (POZEN)	Individual ingredients	Secondary prevention of cardiovascular disease in patients at risk for aspirin-induced ulcers	Antiplatelet activity and proton-pump inhibitor	Headache, dizziness, ecchymosis, flatulence, constipation	Oral	Aspirin portion is delayed-release and the omeprazole portion is immediate release.
Empagliflozin (Boehringer Ingelheim / Eli Lilly and Company)	Canagliflozin	Treatment of type 2 diabetes	Sodium glucose co-transporter-2 (SGLT2) inhibitor	Urinary tract infections, genital infections, pollakiuria, constipation, headache	Oral	
Rizatriptan (IntelGenx)	Triptans	Treatment of migraine headaches	Selective 5-hydroxytryptamine ₁ (5-HT ₁ or serotonin) receptor agonists	Asthenia/fatigue, somnolence, pain/pressure sensation, and dizziness	Oral - film	Submitted as a 505(b)2 new drug application
Simeprevir (TMC435) (Janssen Pharmaceuticals)	Protease inhibitors	Use in combination with pegylated interferon and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients	NS3/4A protease inhibitor	Similar to background therapy with interferon plus ribavirin	Oral	

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

Generic Name Brand Name (Company)	Warning
Bevacizumab <i>Avastin</i> (Genentech Inc)	<p>WARNINGS AND PRECAUTIONS</p> <p>Surgery and Wound Healing Complications</p> <ul style="list-style-type: none"> Necrotizing fasciitis, including fatal cases, has been reported in patients treated with bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation. Discontinue bevacizumab therapy in patients who develop necrotizing fasciitis. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275758.htm</p>
Bupropion hydrochloride <i>Wellbutrin & Wellbutrin SR</i> (GlaxoSmith Kline)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> Increased risk of hypertensive reactions when bupropion is used concomitantly with other drugs that inhibit the reuptake of dopamine or norepinephrine or inhibit their metabolism (eg, MAOIs). Bupropion therapy within 14 days of stopping treatment with an MAOI is also contraindicated. Starting bupropion in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated. <p>ADVERSE REACTIONS</p> <p>Drug Interactions: Updated information regarding the potential interactions with MAOIs or reversible MAOIs (ie, linezolid or methylene blue)</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm267296.htm</p>
Carbamazepine <i>Tegretol</i> (Novartis)	<p>WARNINGS</p> <p>Hypersensitivity Reactions and HLA-A*3101 Allele</p> <ul style="list-style-type: none"> Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLAA*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. Many HLA-B*1502-positive and HLA-A*3101-positive patients treated with carbamazepine will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B*1502-negative and HLA-A*3101-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring, have not been studied. <p>Drug Interactions</p> <p>Agents That May Affect Carbamazepine Plasma Levels</p> <ul style="list-style-type: none"> Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include aprepitant. <p>Effect of Carbamazepine on Plasma Levels of Concomitant</p> <ul style="list-style-type: none"> The leukopenic activity associated with cyclophosphamide therapy may be increased by chronic administration of high doses of CYP3A4 inducer (ie, carbamazepine). When carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled and then adjusted as needed. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced. When carbamazepine is used with tacrolimus, monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are recommended. CYP3A4 inducers such as carbamazepine should be avoided with temsirolimus. The use of carbamazepine with lapatinib should generally be avoided. Dosage adjustment should be considered if lapatinib is coadministered with carbamazepine. If carbamazepine is started in a patient already taking lapatinib, the dose of lapatinib should be gradually titrated up. If carbamazepine is discontinued, the lapatinib dose should be reduced. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm346734.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
Cefepime hydrochloride <i>Maxipime</i> (Hospira)	WARNINGS Neurotoxicity <ul style="list-style-type: none"> • Nonconvulsive status epilepticus http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm323285.htm
Cetuximab <i>Erbitux</i> (Bristol-Myers Squibb)	WARNINGS AND PRECAUTIONS Use of Cetuximab in Combination With Radiation and Cisplatin <ul style="list-style-type: none"> • Cetuximab in combination with radiation therapy and cisplatin increase the incidence of Grade 3–4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone in patients with advanced squamous cell carcinoma of the head and neck. The addition of cetuximab to radiation and cisplatin did not improve progression-free survival. ADVERSE REACTIONS Postmarketing Experience <ul style="list-style-type: none"> • Mucosal inflammation http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289979.htm
Clozapine <i>Clozaril</i> (Novartis)	WARNINGS Metabolic Changes <ul style="list-style-type: none"> • Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. Although atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile. ADVERSE REACTIONS Postmarketing Experience <ul style="list-style-type: none"> • Hepatobiliary system: Hepatotoxicity, hepatic steatosis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, liver injury (hepatic, cholestatic, and mixed), and liver failure • Urogenital system: Renal failure http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm121329.htm
Degarelix <i>Firmagon</i> (Ferring)	WARNINGS AND PRECAUTIONS Hypersensitivity reactions, including anaphylaxis, urticaria, and angioedema, have been reported. Patients with a known history of serious hypersensitivity reactions to <i>Firmagon</i> should not be re-challenged with <i>Firmagon</i> . http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm346725.htm
Infliximab <i>Remicade</i> (Janssen Biotech)	WARNINGS AND PRECAUTIONS Skin cancer <ul style="list-style-type: none"> • Melanoma and Merkel cell carcinoma have been reported in patients treated with tumor necrosis factor (TNF) blocker therapy. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Concurrent Administration With Other Biological Therapeutics <ul style="list-style-type: none"> • There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection. ADVERSE REACTIONS Postmarketing Experience <ul style="list-style-type: none"> • Serious infections and malignancies, including melanoma and Merkel cell carcinoma http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm247032.htm

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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
Meropenem <i>Merrem</i> (AstraZeneca)	<p>WARNINGS AND PRECAUTIONS</p> <p>Potential for Neuromotor Impairment</p> <ul style="list-style-type: none"> Patients receiving meropenem on an outpatient basis may develop adverse events such as seizures, headaches, and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that the drug is well tolerated, patients should not operate machinery or motorized vehicles. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm182235.htm</p>
Metoprolol tartrate <i>Lopressor</i> (Validus Pharmaceuticals)	<p>Heart Failure</p> <ul style="list-style-type: none"> Beta blockers can cause depression of myocardial contractility and may precipitate heart failure and cardiogenic shock. If signs or symptoms of heart failure develop, treat the patient according to recommended guidelines. It may be necessary to lower the dose of metoprolol or to discontinue it. <p>Ischemic Heart Disease</p> <ul style="list-style-type: none"> Do not abruptly discontinue metoprolol therapy in patients with coronary artery disease. Severe exacerbations of angina, myocardial infarction, and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with beta-blockers. <p>Use During Major Surgery</p> <ul style="list-style-type: none"> Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. <p>Bradycardia</p> <ul style="list-style-type: none"> Bradycardia, including sinus pause, heart block, and cardiac arrest, have occurred with the use of metoprolol. Patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders may be at increased risk. Monitor heart rate and rhythm in these patients. If severe bradycardia develops, reduce or stop metoprolol. <p>Exacerbation of Bronchospastic Diseases</p> <ul style="list-style-type: none"> Bronchodilators, including beta2 agonists, should be readily available or administered concomitantly. <p>PRECAUTIONS</p> <p>Risk of Anaphylactic Reactions</p> <ul style="list-style-type: none"> While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge when exposed by accidental, diagnostic, or therapeutic measures. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm192037.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
Nitric oxide inhalation <i>INOMax</i> (INO Therapeutics)	<p>WARNINGS AND PRECAUTIONS</p> <p>Rebound Pulmonary Hypertension Syndrome Following Abrupt Discontinuation Wean From <i>INOMax</i>.</p> <ul style="list-style-type: none"> • Abrupt discontinuation of <i>INOMax</i> may lead to worsening oxygenation and increasing pulmonary artery pressure, ie, rebound pulmonary hypertension syndrome. Signs and symptoms of rebound pulmonary hypertension syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If rebound pulmonary hypertension occurs, reinstate <i>INOMax</i> therapy immediately. <p>Hypoxia from Methemoglobinemia</p> <ul style="list-style-type: none"> • Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen, Methemoglobin levels increase with the dose of <i>INOMax</i>; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of <i>INOMax</i> to optimize oxygenation. <p>Airway Injury from Nitrogen Dioxide</p> <ul style="list-style-type: none"> • Nitrogen dioxide (NO₂) forms in gas mixtures containing NO and O₂. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO₂ in the breathing circuit exceeds 0.5 ppm, decrease the dose of <i>INOMax</i>. • If there is an unexpected change in NO₂ concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO₂ analyzer should be recalibrated. The dose of <i>INOMax</i> and/or FiO₂ should be adjusted as appropriate. <p>Heart Failure</p> <ul style="list-style-type: none"> • Patients with left ventricular dysfunction treated with <i>INOMax</i> may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia, and cardiac arrest. Discontinue <i>INOMax</i> while providing symptomatic care. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm239815.htm</p>
Panitumumab <i>Vectibix</i> (Amgen)	<p>WARNINGS AND PRECAUTIONS</p> <p>Dermatologic and Soft Tissue Toxicity</p> <ul style="list-style-type: none"> • Dermatologic toxicities occurred frequently in patients treated with panitumumab and were severe (NCI-CTC grade 3 and higher) in 16% of patients with metastatic colorectal cancer treated with panitumumab. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. • Monitor patients who develop dermatologic or soft tissue toxicities for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed. Withhold or discontinue panitumumab for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications. <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm165410.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
Sucralfate <i>Carafate Suspension</i> (Aptalis Pharma)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • <i>Carafate</i> is contraindicated for patients with known hypersensitivity reactions to the active substance or to any of the excipients. <p>ADVERSE REACTIONS</p> <p>Post-marketing: Cases of hypersensitivity have been reported with the use of sucralfate suspension, including anaphylactic reactions, dyspnea, lip swelling, edema of the mouth, pharyngeal edema, pruritus, rash, swelling of the face and urticaria</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm239763.htm</p>
Sucralfate <i>Carafate tablet</i> (Aptalis Pharma)	<p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • <i>Carafate</i> is contraindicated for patients with known hypersensitivity reactions to the active substance or to any of the excipients. <p>PRECAUTIONS</p> <ul style="list-style-type: none"> • Isolated reports of sucralfate tablet aspiration with accompanying respiratory complications. Tablets should be used with caution by patients who have known conditions that may impair swallowing, such as recent or prolonged intubation, tracheostomy, prior history of aspiration, dysphagia, or any other conditions that may alter gag and cough reflexes, or diminish oropharyngeal coordination or motility. <p>ADVERSE REACTIONS</p> <p>Postmarketing: Cases of hypersensitivity have been reported with the use of sucralfate suspension, including anaphylactic reactions, dyspnea, lip swelling, edema of the mouth, pharyngeal edema, pruritus, rash, swelling of the face, and urticaria.</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm346722.htm</p>
Ticagrelor <i>Brilinta</i> (AstraZeneca)	<p>CONTRAINDICATIONS</p> <p>Hypersensitivity</p> <ul style="list-style-type: none"> • Contraindicated in patients with hypersensitivity (eg, angioedema) to ticagrelor or any component of the product <p>WARNINGS AND PRECAUTIONS</p> <p>Occasional dyspnea that has required discontinuation (0.9% vs 0.1% of patients taking clopidogrel)</p> <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm338265.htm</p>
Ziprasidone <i>Geodon</i> (Pfizer)	<p>WARNINGS AND PRECAUTIONS</p> <p>Hyperprolactinemia</p> <ul style="list-style-type: none"> • Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density <p>http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm346729.htm</p>

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