Magellan Rx MANAGEMENT

Clinical Alert

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FDA Panel Recommends Cardiovascular Warning for the DPP-4 Inhibitors, Saxagliptin and Alogliptin

Diabetes mellitus affects approximately 29 million people in the United States. People with diabetes are at increased risk for cardiovascular (CV) disease. In 2008, the Food and Drug Administration (FDA) recommended that manufacturers evaluate the CV risk of all new medications used to treat type 2 diabetes during phase 2 and phase 3 trials and long-term (> one year) post-marketing safety studies. The first trials to be completed for diethypeptidyl peptidase-4 (DPP-4) inhibitors, which looked at saxagliptin and alogliptin, are the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus — Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) and the Examination of CArdiovascular OutcoMes with AlogliptIN versus Standard of CarE in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE). On April 14, 2015, the studies were reviewed by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee.

SAVOR was a large, prospective trial that enrolled 16,492 patients with type 2 diabetes who had established CV disease or were at high risk for CV disease. Subjects were followed for a median of 2.1 years. The study showed that saxagliptin (Onglyza®; AstraZeneca) did not increase or decrease the incidence of composite of CV death, nonfatal myocardial infarction (MI), or nonfatal ischemic stroke as compared to placebo. However, a 27% increase in the rate of first hospitalization due to heart failure and a potential increased risk of all-cause mortality was reported with saxagliptin use. The FDA panel voted to revise the saxagliptin label to include the increased risk of heart failure.

EXAMINE enrolled 5,380 patients with type 2 diabetes and acute coronary syndrome (ACS) within the previous three months. This study demonstrated that alogliptin (Nesina®; Takeda) has a similar incidence of composite CV death, nonfatal MI, and nonfatal stroke as placebo. The FDA panel concluded that alogliptin use in patients with type 2 diabetes has an acceptable CV risk profile.

Cardiovascular outcomes studies for other antidiabetic agents are expected to be completed within the next year. Release of a study evaluating CV risk of sitagliptin (Januvia®, Merck Sharp & Dohme) in patients with type 2 diabetes (TECOS) is anticipated in June 2015.

FDA MedWatch: SGLT-2 Inhibitors

The FDA issued a drug safety communication on May 15, 2015, warning that the sodium-glucose cotransporter-2 (SGLT2) inhibitors used to treat type 2 diabetes, canagliflozin (Invokana®; Janssen), dapagliflozin (Farxiga®; AstraZeneca), and empagliflozin (Jardiance®; Boehringer Ingelheim), may lead to ketoacidosis. Twenty cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis were reported to the FDA in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014. All 20 patients required emergency department visits or hospitalization to treat the ketoacidosis. DKA is not an uncommon occurrence in diabetic patients; however, DKA most commonly occurs in patients with type 1 diabetes and is usually accompanied by high serum sugar levels. The cases reported to the FDA were unusual because most of the patients had type 2 diabetes and their blood sugar levels, when reported, were only slightly increased compared to typical cases of DKA. Healthcare providers are urged to monitor patients receiving a SGLT2 inhibitor closely for signs of ketoacidosis, including difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. The FDA continues to investigate this issue to decide

Drug Information Highlights

- The FDA approved a label change to remove the indication for combined use with a statin from niacin ER (Niaspan®) and fenofibric acid (Trilipix®). Niacin ER is no longer indicated in combination with simvastatin or lovastatin for the treatment of primary hyperlipidemia or mixed dyslipidemia when treatment with monotherapy is inadequate. Niacin ER is still indicated to treat dyslipidemia and hypertriglyceridemia, to reduce the risk of recurrent MI in patients with hyperlipidemia, and in combination with a bile acid resin for the treatment of atherosclerosis. Fenofibric acid is no longer indicated as an adjunct to diet in combination with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent on optimal statin therapy. Trilipix is still appropriate as monotherapy for the treatment of severe hypertriglyceridemia, primary hypercholesterolemia, or mixed dyslipidemia.
- On May 22, 2015, the US Court of Appeals ordered Actavis to continue sales of their Alzheimer's agent, Namenda® (memantine) immediate-release (IR) tablet, until August 10, 2015. This decision allows patients to continue treatment with the product until the availability of generic memantine IR tablets, expected to be launched as early as July 11, 2015. Recommended dosing of Namenda® IR is twice daily. Actavis also distributes Namenda oral solution dosed twice daily and the once-daily extended-release formulations, Namenda XR® (memantine) and Namzaric® (memantine/donepezil), for the treatment of Alzheimer's type dementia.
- Concomitant use of the PDE5 inhibitors used for the treatment of pulmonary arterial hypertension (PAH), sildenafil (Revatio®) or tadalafil (Adcirca®), with a guanylate cyclase (GC) stimulator (e.g., riociguat [Adempas®]) is now contraindicated as these agents may potentiate the hypotensive effects of GC stimulators.
- The FDA approved labeling revisions for all stimulant products approved for the treatment of attention deficit hyperactivity disorder (ADHD) to include post-marketing reports of rhabdomyolysis. There is an association between the use of stimulants used to treat ADHD and rhabdomyolysis.
- Boxed warning revisions have been made for itraconazole (Sporanox®) capsules and oral solution. The following drugs were added to

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if any change to the labeling of the SGLT2 inhibitors is necessary. Side effects involving SGLT2 inhibitors should be reported to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page on the FDA website (www.fda.gov).

American Academy of Pediatrics Treatment Guidelines for Head Lice

The American Academy of Pediatrics (AAP) released an update to the 2010 clinical report on the treatment of head lice which provides information to healthcare providers on the safe and effective treatment of head lice, including information on new products. The 2015 guidelines maintain that, in the absence of resistance in the community, treatment of an active head lice infestation should be initiated with either permethrin 1% or pyrethrins, available over-the-counter (OTC). For locations where resistance is present, benzyl alcohol 5% is recommended for children older than six months, and malathion 0.5% (Ovide®) is safe and effective for children six years or older; AAP advises that malathion is contraindicated in children younger than 24 months. These agents may also be used in patients that have failed to respond to appropriately administered therapy with permethrin or pyrethrins. New agents added to the guidelines include spinosad (Natroba™; ParaPRO) and topical ivermectin (Sklice®; Sanofi), which may be useful for difficult to treat cases. Instructions regarding the proper use of pediculosides should be followed carefully, including at least two appropriately timed applications of the product if permethrin of pyrethrins are used for treatment. Excessive home cleaning with pesticides is not required; however, washing pillow cases and hair brushes is recommended. As previously, the AAP emphasize that, while head lice is a nuisance, it is not a serious disease or sign of poor hygiene. No healthy child should be required to miss time at school because of head lice or nits and schools should be encouraged to abandon "no-nit" policies.

Management of First Seizure in Adults

The American Academy of Neurology (AAN) and the American Epilepsy Society (AES) released evidence-based guidelines on the prognosis and treatment of a first unprovoked seizure in adults. The guideline discusses three questions related to adults with a first unprovoked seizure: (1) What are the risks for seizure recurrence after a first seizure?; (2) Does immediate treatment with an anti-epileptic drug (AED) reduce or change the short-term risks for a seizure recurrence or the long-term prognosis for seizure freedom or remission?; and (3) For those patients prescribed AEDs immediately, what are the risks for adverse events?.

Adults with an unprovoked first seizure should be informed that:

- The greatest risk of seizure recurrence is within the first two years. Factors associated with an increased risk of seizure recurrence include a prior brain injury, electroencephalogram (EEG) epileptiform abnormalities, significant abnormality on brain-imaging, or the occurrence of a nocturnal seizure.
- Compared to delaying treatment until after the occurrence of a second seizure, immediate AED therapy is likely to reduce the risk of recurrence within the first two years; however, it may not be associated with an improvement in the quality of life. Over a longer term period (> three years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
- The risk for adverse events from AED therapy ranges from 7% to 31% with the adverse events generally being mild and reversible.

When determining whether to initiate immediate AED treatment after a first unprovoked seizure, clinicians should consider the risk of seizure recurrence against the risk of adverse events of AED therapy, educated patient preferences, and that immediate treatment will not improve the long-term prognosis for seizure remission, but will reduce seizure risk over the first two years.

the list of agents that are contraindicated when administered with itraconazole: ticagrelor, fesoterodine, telithromycin, and solifenacin. The revised boxed warning also states that itraconazole should not be administered in patients with congestive heart failure.

- Additional language has been added to the label for the oral multiple sclerosis agent, fingolimod (Gilenya®; Novartis), to include trial data regarding the incidence of bradyarrhythmia and atrioventricular blocks, herpes viral infections, macular edema, respiratory effects, and liver injury.
- The FDA has expanded the indication for sumatriptan/naproxen tablets (Treximet®; Pernix) to include patients 12 years and older for the acute treatment of migraine with or without aura. Treximet was previously only for use in patients 18 years of age and older.
- The FDA has updated the breakthrough therapy designation for Bristol-Myers-Squibb's (BMS's) pipeline drug daclatasvir used in combination with Gilead's sofosbuvir (Sovaldi®). The updated designation reflects recently presented data from the ALLY-1 trial on hepatitic C virus (HCV) genotype 1 infection in patients with advanced cirrhosis (Child-Pugh Class B or C) and those who develop genotype 1 HCV recurrence post-liver transplant. This updated designation does not affect the FDA's ongoing new drug application (NDA) review of BMS' daclatasvir-sofosbuvir regimen for the treatment of patients with genotype 3 HCV.
- Moxifloxacin (Avelox®; Bayer) has received an expanded indication to include treatment and prophylaxis of plague due to *Yersinia pestis* in adult patients. Moxifloxacin is also indicated to treat infections of the respiratory tract, skin and abdomen due to susceptible organisms.

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **June 13, 2015:** Zubsolv®; buprenorphine/naloxone; partial opioid agonist/opioid antagonist sublingual tablet; induction treatment for opioid dependence; Orexo.
- **June 23, 2015:** Kengreal; cangrelor; intravenous $P2Y_{12}$ platelet inhibitor; reduction of thrombotic CV events in patients with coronary artery disease undergoing percutaneous coronary intervention; The Medicines Company.
- **June 29, 2015:** oral oxycodone; abuse-deterrent formulation; pain; Purdue.
- **2nd Quarter 2015:** cariprazine; oral dopamine receptor partial agonist; manic/mixed treatment of bipolar disorder, schizophrenia; Gedeon Richter USA/Actavis.

Digoxin-associated Mortality Risk

Digoxin has been used for many years for the treatment of congestive heart failure (CHF) and atrial fibrillation (AF); however, conflicting data exist on the effect of digoxin use on the mortality of patients with CHF and/or AF. The results of a meta-analysis published online on May 4, 2015, in the *European Heart Journal* evaluated the effects of digoxin on death from any cause in patients with AF and CHF. The meta-analysis reviewed 19 studies which contained a total of 326,426 patients. Overall, digoxin use was associated with a 21% increased relative risk of all-cause mortality; a 29% increase in patients with AF and 14% increase in patients with heart failure. These results are based on the largest review of evidence for digoxin to date and indicate that digoxin is associated with an increased risk of death in this patient population, particularly in those with AF.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
methylphenidate extended-release	Aptensio XR™	The FDA has approved methylphenidate extended-release (Aptensio XR), a central nervous system (CNS) stimulant and Schedule II controlled substance, for the treatment of ADHD. Aptensio XR is available as 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg extended-release capsules. Daily dosage above 60 mg is not recommended. Aptensio XR has both an immediate-release and a controlled-release layer, containing approximately 40% and 60% of the methylphenidate dose, respectively. The relative bioavailability of Aptensio XR once daily is comparable to methylphenidate immediate-release given three times daily. The recommended starting dose for patients six years of age and older is 10 mg once daily, with or without food, in the morning. Capsules may be opened and contents sprinkled onto applesauce. Contraindications and warnings are similar to those of other CNS stimulants.	Rhodes	FDA NDA Approval 04/17/2015
deoxycholic acid	Kybella™	Deoxycholic acid (Kybella), a cytolytic drug, is the first non-surgical treatment to be approved by the FDA for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (double chin) in adults. The use of deoxycholic acid for the treatment of subcutaneous fat outside the submental region has not been FDA approved and is not recommended. Kybella is a non-human and non-animal formulation of endogenous deoxycholic acid, which aids the body in the breakdown and absorption of dietary fat. Deoxycholic acid, approved as a 20 mg/2 mL single patient use vial, is to be administered only by a healthcare professional into subcutaneous fat tissue in the submental region using an area-adjusted dose of 2 mg/cm^2. One treatment can consist of up to fifty 0.2 mL injections spaced 1 cm apart. A maximum of six single treatments may be administered at sessions at least one month apart. Marginal mandibular nerve injury, dysphagia, and bruising may occur with use. Kythera's training program is scheduled to launch in late summer 2015 to educate providers on the safe use of deoxycholic acid. Physicians will be able to purchase deoxycholic acid for patient use after completing the training. Kybella is for cosmetic use only.	Kythera	FDA NDA approval 04/29/2015
codeine / chlorpheniramine	Tuzistra™ XR	The FDA has approved the combination product of codeine, an opiate agonist antitussive, and chlorpheniramine, a histamine-1 receptor antagonist (Tuzistra XR), for the relief of cough and symptoms associated with upper respiratory allergies or the common cold in adults. Tuzistra XR, a Schedule III controlled substance, is the only codeine-based extended-release oral suspension to be available on the market. Tuzistra XR contains 14.7 mg of codeine polistirex (equivalent to 20 mg codeine phosphate) and 2.8 mg of chlorpheniramine polistirex (equivalent to 4 mg chlorpheniramine maleate), per 5 mL respectively and is dosed as 10 mL every 12 hours.	Tris	FDA NDA approval 04/30/2015
fluticasone furoate / vilanterol	Breo® Ellipta®	Fluticasone furoate/vilanterol (Breo Ellipta), a fixed-dose combination of an inhaled corticosteroid and long-acting beta$_2$ agonist, is now indicated for the once-daily treatment of asthma in adults. Breo Ellipta powder for oral inhalation is available as 100 mcg/25mcg and 200 mcg/25 mcg of fluticasone furoate and vilanterol, respectively. The recommended dosage for asthma treatment is one inhalation, of either strength, once daily. Breo Ellipta is already indicated for long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).	GlaxoSmith Kline	FDA NDA approval 04/30/2015
paliperidone palmitate	Invega Trinza™	Paliperidone palmitate (Invega Trinza), a 3-month injectable atypical antipsychotic, has been approved by the FDA for the treatment of schizophrenia in patients after they have been adequately treated with Invega Sustenna® (1-month paliperidone palmitate) for at least four months. Invega Trinza is administered once every three months by intramuscular injection by a healthcare professional only. It will be available as an extended-release injection suspension in 273 mg, 410 mg, 546 mg, and 819 mg strengths. Contraindications and warnings are similar to other antipsychotics, including the boxed warning for increased mortality in elderly patients with dementia-related psychosis. Invega Trinza is scheduled to be commercially available by mid-June 2015.	Janssen	FDA NDA priority approval 05/18/2015

References
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