Magellan Rx MANAGEMENT

Clinical Alert

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Empagliflozin Gains Cardiovascular (CV) Risk Reduction Indication

Empagliflozin (Jardiance®; Boehringer Ingelheim), which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), has received a new indication. The oral sodium-glucose co-transporter 2 (SGLT2) inhibitor, empagliflozin has been approved for the reduction of risk of CV death in adults with T2DM and established cardiovascular disease (CVD). This new indication is based on positive results of the EMPA-REG OUTCOME landmark trial that evaluated the CV benefit and safety of empagliflozin as add-on to standard-of-care in over 7,000 patients with T2DM and CVD. Empagliflozin led to a 14% relative reduction in the first occurrence of a major CV event (composite of CV death, nonfatal myocardial infarction [MI], nonfatal stroke) and was deemed superior to placebo. This reduction was almost entirely due to an impact on CV death (38% reduction); the drug was not shown to significantly reduce nonfatal MI or nonfatal stroke.

Empagliflozin is the first antidiabetic agent approved by the Food and Drug Administration (FDA) to reduce CVD risk. The injectable glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide (Victoza®; Novo Nordisk), also demonstrated CV benefit in patients with T2DM. The LEADER trial reported a 13% relative reduction in first occurrence of major coronary event (death from CV cause, nonfatal MI, or nonfatal stroke) with liraglutide. Likewise, the benefit was mostly due to reduction in death from CV or other causes. Novo Nordisk is seeking an indication for CVD risk reduction for liraglutide; FDA decision is expected in 2017.

Mylan Launches First Authorized Generic for Epipen®

Mylan, the manufacturer of Epipen, announced the much-awaited launch of the authorized generic, epinephrine injection USP. The authorized generic contains the same device functionality, drug formulation, and administration as the brand name Epipen auto-injector. Compared to Epipen, the authorized generic wholesale acquisition cost (WAC) is approximately 50% lower. The authorized generic became available in 0.15 mg and 0.3 mg strengths starting the week of December 19, 2016 to retail pharmacies. Similar to Epipen, the authorized generic is available as a package containing 2 auto-injectors; patients with a history of anaphylaxis are advised to carry 2 ephinephrine auto-injectors to allow for a repeat injection if persistent anaphylaxis occurs.

An authorized generic for Impax's Adrenaclick® brand epinephrine auto-injector is also available. It is not considered therapeutically equivalent to Epipen or the authorized generic for Epipen. The WAC price for Impax's authorized generic is approximately 30% higher than Mylan's authorized generic. Brand Adrenaclick is no longer manufactured. Furthermore, Kaleo plans to reintroduce Auvi-Q®, an epinephrine auto-injector with visual and audio administration cues, to the market during the first half of 2017. Auvi-Q was recalled in October 2015 due to potentially inaccurate dosage delivery.

ADA's Standards of Medical Care in Diabetes - 2017

The American Diabetes Association (ADA) has released their annual update for their Standards of Medical Care in Diabetes. This addresses psychosocial issues in all aspects of diabetes care including self-management, mental health, communication,

Drug Information Highlights

- The first generic for Zetia® (ezetimibe) 10 mg oral tablets was approved by the FDA. Ezetimibe inhibits the absorption of cholesterol in the intestine. It is indicated as adjunct to diet for the management of primary or mixed hyperlipidemia, homozygous familial hypercholesterolemia (HoFH), and homozygous sitosterolemia. It is used either alone or in combination with a statin or fenofibrate, depending on the condition being treated.
- Novo Nordisk's long-acting insulin analog, insulin degludec (Tresiba®), was approved for an expanded indication to improve glycemic control in patients 1 year of age and older with type 1 or type 2 diabetes. It is administered subcutaneously once daily at any time of day. Pediatric patients 1 year or older should be started at a dose that is 80% of the total daily long- or intermediate-acting insulin dose to minimize the risk of hypoglycemia. Insulin degludec is not recommended in pediatric patients who require a dose < 5 units. It is available as 100 unit/mL and 200 unit/mL concentrations in 3 mL FlexTouch® prefilled pens.
- Bevacizumab (Avastin®), a vascular endothelial growth factor-specific angiogenesis (VEGF) inhibitor by Genentech, received approval for use in combination with carboplatin plus either paclitaxel or gemcitabine, followed by bevacizumab as a single agent, to treat platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Dosage for the new indication is 15 mg/kg intravenously (IV) every 3 weeks as combination therapy, followed by bevacizumab 15 mg/kg IV every 3 weeks alone. Combination therapy is given for 6 to 8 weeks for paclitaxel-containing regimens, and for 6 to 10 weeks for gemcitabine-containing regimens. Bevacizumab is also indicated for the treatment of platinum-resistant cancer of the ovary, fallopian tube, and peritoneum, in addition to glioblastoma, non-squamous non-small cell lung cancer, and metastatic colorectal cancer and renal cell carcinoma.
- Mylan announced their decision to discontinue Miacalcin® nasal spray (200 IU/spray) as a multidose container with pump. The manufacturer states that this decision is for business reasons, and the discontinuation is not related to the quality, safety, or efficacy of the product. Generic formulations of calcitonin-salmon nasal spray are available.

complications, comorbidities, and life-stage considerations. The following is a summary of select revisions:

- A new section was added on "Comprehensive Medical Evaluation and Assessment of Comorbidities," with an expanded list of diabetes comorbidities now including autoimmune diseases, HIV-infection, anxiety disorders, depression, disordered eating behavior, and serious mental illness.
- Recommendations for patients prescribed flexible insulin therapy were updated to include fat and protein counting in addition to carbohydrate counting to reflect that these dietary factors influence blood glucose levels and insulin dosing.
- Serious, clinically significant hypoglycemia is now defined as serum glucose < 54 mg/dL, while the glucose "alert" value is defined as ≤ 70 mg/dL. This is based on recommendations from the International Hypoglycemia Study Group.
- A recommendation was added to consider empagliflozin or liraglutide in patients with T2DM and established CVD to reduce mortality risk based on the results of clinical trials.
- The algorithm for the use of combination injectable therapy in patients with T2DM has been updated to reflect recent studies and provide several pathways using insulin to meet glycemic goals in patients with T2DM.
- Insulin was emphasized as the treatment of choice in pregnancy based on concerns with both metformin and glyburide.
- Due to concerns about the affordability of antidiabetic therapy, new tables were added to display the median average wholesale costs (AWP) of insulin and non-insulin agents. Newly available follow-on insulins have also been included (e.g., Eli Lilly's Basaglar®, a follow-on to Sanofi's insulin glargine U-100, Lantus®).

The complete 2017 Standards of Care document is available at: www.diabetes.org.

FDA Drug Safety Communication: Updated Review of Pioglitazone and Risk of Bladder Cancer

In September 2010 and June 2011, the FDA issued drug safety communications regarding the possible risk of bladder cancer with use of pioglitazone. These alerts were based on 5-year interim study results of a 10-year epidemiologic study that was conducted by the manufacturer of pioglitazone (Actos®), Takeda Pharmaceuticals. In August 2011, the labels of all pioglitazone-containing products were modified to include warnings about the risk of bladder cancer. On December 12, 2016, the FDA released a new drug safety communication regarding pioglitazone and the risk of bladder cancer. The FDA reviewed the final 10-year study results, as well as other published studies, regarding the risk of pioglitazone and bladder cancer. In the 10-year final results of the epidemiologic study, use of pioglitazone was not associated with a significantly increased risk for bladder cancer. However, other published studies show conflicting results regarding bladder cancer risk. As a result of this updated review, the FDA concluded that use of pioglitazone may be linked to an increased risk of bladder cancer.

Labeling for all pioglitazone-containing products (Actos, Actoplus Met®, Actoplus Met XR®, Duetact®, Oseni®) has been updated to include the additional studies. Healthcare professionals (HCP) are advised to not use pioglitazone in patients with active bladder cancer and to carefully consider the risks in patients with a history of bladder cancer.

AACE/ACE Relabels Obesity

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published a position statement redefining and relabeling the term obesity (defined as body mass index [BMI] ≥ 30 kg/m^2) as adiposity-based chronic disease (ABCD). This new diagnostic term identifies ABCD as a chronic disease, implies a specific pathophysiological basis, and avoids the stigma and confusion related to the term 'obesity'. The quantity of body fat mass can be associated with adverse clinical endpoints, but is not reliably reflected by BMI, which does not take into account measures, such as waist circumference, muscle mass, and ethnic variations. The position statement emphasizes physiologic effects of weight excess. AACE/ACE categorize severity of adiposity-based complications; stage 0 = none identified, stage 1 = mild to moderate, and stage 2 = severe. Individualized care plans should include structured lifestyle medicine (non-drug and non-surgical approaches) to promote health, and standardized protocols that address weight loss and adiposity–based complications. Pharmacotherapy and endoscopic and bariatric procedures can be considered based on adiposity-severity.

- The FDA removed the boxed warning regarding drug-drug interactions for patiromer oral suspension (Veltassa®; Relypsa). Patiromer is a potassium binder used to treat non-life-threatening hyperkalemia. The drug label still advises that patiromer can bind to other oral medications, resulting in decreased gastrointestinal absorption and efficacy; however, the time period recommended between dosing of patiromer before/after other oral medications was reduced from 6 hours to 3 hours.
- The leukemia drug, ponatinib (Iclusig®; Ariad), received multiple expanded indications. It is now approved to treat adults with chronic-, accelerated-, or blast-phase chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other tyrosine kinase inhibitor (TKI) agent is indicated. The FDA also approved ponatinib use in adults with T315I-positive CML (in the same phases as listed above) and T315I-positive Ph+ ALL.
- Shire's IV recombinant coagulation factor VIII, Adynovate®, received an expanded indication to include treatment of hemophilia A in children < 12 years of age. It is used as on-demand treatment of bleeding episodes (dose based on patients factor VIII level) and routine prophylaxis (40-50 IU/kg twice a week).

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

- **January 2017:** infliximab, biosimilar to Janssen's Remicade®; IV tumor necrosing factor (TNF)-α inhibitor; rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease, plaque psoriasis, psoriatic arthritis, ulcerative colitis; Samsung Bioepis/Merck/Biogen.
- **January 11, 2017:** Varubi® (IV); rolapitant; IV neurokinin-1 (NK1) receptor antagonist; chemotherapy-induced nausea and vomiting (CINV); Tesaro/OPKO Health.
- **January 19, 2017:** baricitinib; oral Janus kinase (JAK) inhibitor; RA; Eli Lilly/Incyte.
- **January 29, 2017:** plecanatide; oral guanylate cyclase stimulant; chronic idiopathic constipation (CIC); Synergy.
- **January 31, 2017:** hydrocodone/acetaminophen/promethazine; oral fixed-dose combination opioid agonist, COX inhibitor, H1-histamine antagonist; moderate to severe acute pain with prevention of opioid induced nausea and vomiting; Charleston Labs/Daiichi Sankyo.
- **February 2017:** deflazacort; oral glucocorticoid; Duchenne muscular dystrophy; Marathon.
- **February 2017:** MK-8237; sublingual immunotherapy (house dust mite); allergic rhinitis; Merck/ALK-Abello.
- **Half 1, 2017:** oxymetazoline HCl 1% cream; topical anti-inflammatory; rosacea; Allergan.

FDA Drug Safety Communication: Anesthesia and Sedation

The FDA released a Drug Safety Communication warning of the risk of use of general anesthetic or sedation drugs in young children or pregnant women. When used for more than 3 hours, general anesthetic and sedation drugs were found to cause widespread loss of nerve cells in the brains of pregnant and young animals. Studies in both animals and humans show that relatively short exposure to these drugs is unlikely to have a negative affect on a child's behavior or learning; however, further research is warranted. The FDA Drug Safety Communication warns that repeated or prolonged duration of the use of general anesthetic or sedation drugs may affect brain development in children less than 3 years old or when used in pregnant females during the third trimester. The FDA is requiring the labels of general anesthetic and sedation drugs to be updated with warnings regarding this risk. HCPs are encouraged to weigh the benefits of anesthesia in young children and pregnant women against the potential risks, especially for procedures that exceed a 3-hour duration or if multiple procedures are required in children under 3 years.

The American College of Obstetricians and Gynecologists (ACOG) has significant concerns over the FDA advisory. ACOG states that loss of nerve cells can happen between 5 and 24 hours of exposure to anesthetic and sedative agents, rather than 3 hours as reported by the FDA. ACOG also maintains that pregnant women in any trimester should be counseled on the risks and benefits and of any proposed intervention that requires the use of general anesthesia or sedation. According to ACOG, no women should be denied surgery or a procedure that requires the use of these drugs.

Second-Generation Antipsychotics (SGA) and Treatment-Resistant Depression

There is no consensus definition of treatment-resistant depression; however, most published definitions imply either no response or an inadequate response to appropriate therapy. Either a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) is generally used first-line to treat depression and are effective with continuous use (4 to 9 months) to treat major depressive disorder (MDD). A number of other medications, such as some newer (e.g., vilazodone and vortioxetine) and some older (e.g., bupropion and mirtazapine) antidepressants, could be used. If a patient's depression appears to be resistant to therapy, clinicians should assess the accuracy of the diagnosis, adherence to the current treatment, and possible abuse of alcohol or drugs and should confirm that past treatment trials have been adequate in terms of both duration and dose. Adjunctive use of a SGA agent may also be considered for treatment-resistant depression.

Multiple positive, placebo-controlled studies have been conducted for 4 SGAs, including the 3 drugs that have been approved by the FDA for a specific indication (aripiprazole [Abilify®], quetiapine [Seroquel®], and olanzapine [Zyprexa®]) and a fourth (risperidone [Risperdal®]) that was studied but not evaluated by the FDA for this indication. A fifth SGA (brexpiprazole [Rexulti®]) was approved by the FDA based on 2 positive studies. Research has not identified an ideal duration of adjunctive antipsychotic therapy. Given known side effects of these medications, tapering the adjunctive SGA within 2 or 3 months if clinically feasible may be a reasonable strategy. Notably, SGAs could be considered for treating antidepressant nonresponse; the potential benefits must be carefully balanced against the adverse effects risk, although often manageable, and increased cost.

Use of Antipsychotics for Dementia-Related Agitation or Psychosis

In 2016, the American Psychiatric Association (APA) released a practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. The guidance applies to individuals with dementia in all settings. Fifteen guideline statements are provided, covering assessment of symptoms of dementia, development of a comprehensive treatment plan, assessing benefits and risks of treatment, dosing and monitoring of antipsychotic therapy as well as use of specific antipsychotics in varying clinical context. APA recommends, after review of risks and benefits, nonemergency antipsychotic medication for severe, dangerous, or distressful symptoms of agitation or psychosis. Antipsychotic therapy should be started at a low dose and titrate up to the minimum effective tolerable dose. If no clinically significant response is seen after 4 weeks, the patient should be tapered off the antipsychotic agent. For patients who experience an adequate response, an attempt to taper off the antipsychotic should be made after 4 months of treatment initiation. During taper, patients should be assessed for signs of recurrence at least monthly and for at least 4 months after discontinuation. APA recommends against use of haloperidol as first-line and state that a long-acting injectable antipsychotic should only be used if it is indicated for a co-occurring chronic psychotic disorder. The full guidelines are available at: http://psychiatryonline.org.

Boxed Warnings Removed for Chantix® and Zyban®

The FDA has removed the boxed warnings of mental health adverse effects from the labeling of varenicline (Chantix) and bupropion (Zyban), 2 drugs used to help people stop smoking. This decision was based on results from mandatory large clinical studies conducted by the drug manufacturers in patients with and without a history of psychiatric disorders. The results demonstrated a lower risk of serious side effects on mood, behavior, or thinking than previously reported. In the studies, patients received varenicline or bupropion for 12 weeks, followed by 12 weeks of follow-up. The incidence of neuropsychiatric adverse effects was similar across treatment groups in patients without a history of psychiatric illness (approximately 3%). There was a higher incidence of neuropsychiatric adverse effects in patients with a psychiatric disorder across all treatment groups; risk was numerically higher in patients treated with varenicline or bupropion compared to placebo (12.2% versus 9.5%). The FDA still notes that neuropsychiatric effects are possible but concluded that the benefits of smoking cessation outweigh the risks of these products. Patients taking varenicline or bupropion should notify their HCP immediately if they experience changes in mood, behavior, or thinking.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
prasterone	Intrarosa™	The steroid prasterone, also known as dehydroepiandrosterone (DHEA), received approval for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The vaginal insert, containing 6.5 mg of prasterone, is to be inserted once daily at bedtime using the provided applicator. A warning exists for women with current or past history of breast cancer, as estrogen is a metabolite of prasterone, and the use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. The most common adverse drug reactions are vaginal discharge and abnormal Pap smear.	Endoceutics	FDA NDA approval 11/16/2016
empagliflozin/ metformin extended-release (ER)	Synjardy® XR	Synjardy XR, a fixed-dose combination of the SGLT2 inhibitor empagliflozin and metformin ER, a biguanide, has been approved in a once daily formulation. It is indicated as adjunct to diet and exercise to improve glycemic control in patients with T2DM when treatment with both empagliflozin and metformin is appropriate. It carries a boxed warning for the potential risk of lactic acidosis due to the metformin component. It is approved as tablets containing 25 mg of empagliflozin and 2,000 mg of metformin ER. Synjardy® is available as oral tablets containing empagliflozin and metformin immediate-release, for twice-daily dosing. Its indication is the same as Synjardy XR. Empagliflozin recently gained the indication to reduce the risk of CV death in adults with T2DM and established CVD. However, the effectiveness of Synjardy XR on reducing the risk of CV death in adults with T2DM and CVD has not been established.	Boehringer Ingelheim	FDA NDA approval 12/09/2016
crisaborole	Eucrisa™	The FDA approved crisaborole (Eucrisa), a phosphodiesterase 4 (PDE-4) inhibitor, for the treatment of mild to moderate atopic dermatitis (eczema) in patients 2 years of age and older. Approved as a 2% ointment, crisaborole is applied topically, as a thin layer, to affected areas twice daily. The most common adverse reaction with use of crisaborole is application site pain, which was reported in 4% of patients in clinical trials.	Anacor	FDA NDA approval 12/14/2016
rucaparib	Rubraca™	The agency granted approval for the poly (ADP-ribose) polymerase (PARP) inhibitor, rucaparib (Rubraca), as monotherapy for the treatment of deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer in patients, as selected based on FDA-approved companion test, who have been treated with at least 2 lines of chemotherapy. Median duration of response was 9.2 months. Rucaparib was approved under accelerated approval; continued approval for this indication may depend upon results of confirmatory trials. The product is approved as 200 mg and 300 mg oral tablets. Recommended dose is 600 mg twice daily without regard to food intake. Dose interruption or reduction may be considered to manage side effects. The most common adverse reactions reported (≥ 20%) were gastrointestinal in nature. Treatment is continued until disease progression or unacceptable toxicity. The FoundationFocus CDx_{BRCA}™ was also FDA approved as a companion diagnostic test.	Clovis Oncology	FDA NDA accelerated approval 12/19/2016
nusinersen	Spinraza™	Nusinersen (Spinraza), a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide has been approved. Granted fast track and orphan drug designations, as well as rare pediatric disease priority review, it is the first drug approved to treat spinal muscular atrophy (SMA), a rare and often fatal genetic condition in children and adults characterized by progressive muscle weakness and impaired movement. In clinical trials, 40% of patients treated with nusinersen experienced improvement in predefined motor milestones, compared to none in patients treated with placebo. Nusinersen is administered intrathecally over 1 to 3 minutes. Recommended dose is 12 mg given as the first 3 doses every 14 days, followed by the fourth dose given 30 days after the third dose, then maintenance doses every 4 months thereafter. It is approved as a 12 mg/15 mL single-dose vial. Thrombocytopenia, coagulation abnormalities, and renal toxicity have been reported in clincal trials. The most common adverse effects (≥ 20%) include respiratory tract infections and constipation.	Biogen	FDA NDA priority approval 12/23/2016

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