Magellan Rx MANAGEMENT

Clinical Alert

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FDA Approves Second PCSK9 Inhibitor for Hyperlipidemia

Amgen's evolocumab (Repatha™) has received Food and Drug Administration (FDA) approval as adjunct therapy to diet and maximally tolerated statins in adults with clinical atherosclerotic cardiovascular disease (CVD), heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH), who require additional lowering of low density lipoprotein cholesterol (LDL-C). HeFH and HoFH are inherited lipid disorders. Evolocumab is the second drug in the class of proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitors, which increase the ability of hepatocytes to clear LDL-C from the blood.

In phase 3 clinical trials, patients treated with evolocumab experienced an average LDL-C reduction of approximately 30% to 70%. Evolocumab is approved as 140 mg/mL single-use prefilled syringe and SureClick® autoinjector that allow for self-administration. The recommended dose is 140 mg subcutaneously (SC) every two weeks or 420 mg once monthly to treat HeFH or clinical atherosclerotic CVD (primary hyperlipidemia); and 420 mg SC once monthly to treat HoFH. The 420 mg dose is administered as three 140 mg injections consecutively within 30 minutes; Amgen plans to make a single injection monthly option available in 2016.

The most common adverse effects are generally mild to moderate and include nasopharyngitis, upper respiratory tract infection, influenza, and back pain. Injection site reactions occurred in 5.7% of patients. Neurocognitive effects, such as transient confusion and memory loss, which have been described in patients on chronic statin therapy, have been reported in 0.2% of patients treated with evolocumab. Since evolocumab is a fully human monoclonal antibody, the development of anti-drug neutralizing antibodies could be a potential future concern.

Statins remain the drugs of choice for lowering LDL-C and preventing cardiovascular (CV) events, even in patients with HoFH. However, PCSK9 inhibitors offer another option to reduce LDL-C levels when maximum statin therapy alone does not provide desired LDL-C reduction or is not tolerated. Sanofi/Regeneron's PCSK9 inhibitor, alirocumab (Praluent®) was FDA approved in July 2015 for the treatment of adults with HeFH or clinical atherosclerotic CVD as an adjunct to diet and maximally tolerated statin therapy and is dosed SC every two weeks. Pfizer's bococizumab is currently in phase 3 clinical trials and could be available in 2016.

The effects of evolocumab and alirocumab on CV morbidity and mortality have not been determined; studies for each drug are ongoing. Alirocumab is also being studied for once monthly dosing.

First Drug Utilizing 3D Printing Technology is FDA Approved

On July 31, 2015, the FDA approved Aprecia Pharmaceuticals' antiseizure agent, levetiracetam (Spritam®), marking the first approval of a drug utilizing three-dimensional printing (3DP) technology. Spritam is indicated for adjunctive therapy in the treatment of partial onset seizures in patients 4 years of age and older who weigh more than 20 kg; myoclonic seizures in patients at least 12 years or age; and primary generalized tonic-clonic seizures in patients 6 years and older. As other levetiracetam products, Spritam is dosed twice daily and is approved as 250 mg, 500 mg, 750 mg and 1,000 mg oral tablets.

Drug Information Highlights

- The FDA has alerted that one confirmed case and one probable case of the serious brain infection, progressive multifocal leukoencephalopathy (PML) have been reported in patients taking fingolimod (Gilenya®). Both cases included patients who had not been previously treated with an immunosuppressant agent. As reported in a prior Clinical Alert newsletter, Novartis had previously notified the FDA of these cases. As a result, information has been added to the Warnings and Precautions and Patient Counseling Information sections of the fingolimod label.
- A warning has been issued by the FDA that reports of name confusion between the antidepressant, vortioxetine (Brintellix®) and the antiplatelet agent, ticagrelor (Brilinta®) that has resulted in the wrong medication being prescribed or dispensed. The FDA is advising health care professionals (HCP) to reduce the risk of name confusion by including both the generic and brand names of the medication and the indication for use when prescribing these agents.
- Oxycodone extended-release oral tablets (OxyContin®; Purdue) received an expanded indication for severe pain that requires daily, around-the-clock, long-term opioid treatment for opioid-tolerant pediatric patients aged 11 years and older. Opioid-tolerant pediatric patients are defined as those already receiving and tolerating at least 20 mg oxycodone orally or the equivalent. OxyContin was previously indicated only for adult opioid-tolerant patients. Detailed dosing and conversion information is contained in the label. Safety and efficacy of other oxycodone-containing products have not been established in pediatric patients.
- During 2015, Otsuka voluntarily discontinued marketing of the oral solution, oral disintegrating tablet (Discmelt®), and injection formulations of their antipsychotic drug Abilify® (aripiprazole). The 15 mg Discmelt tablets are still available; however, supply is expected to be depleted by the end of November 2015. Abilify oral tablet will remain on the market. This discontinuation is not related to safety or efficacy; therefore, generic versions are eligible for FDA approval.
- The FDA has issued a warning of severe allergic reactions and herpes zoster (shingles) reactivation with the use of ingenol mebutate (Picato®; Leo), indicated for the topical

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Spritam is a quick dissolving tablet with equivalent rate and extent of absorption to levetiracetam immediate-release tablets (Keppra®). Warnings and adverse reaction profiles are similar to other levetiracetam products. For further details, please refer to the complete prescribing information at www.spritam.com.

Three-dimensional printing technology was developed in the 1980s at the Massachusets Institute of Technology (MIT). Three-dimensional printers create a product by layering materials until a 3D object is formed. In the years since its development, 3DP technology has been used in dentistry to create replicas of jaws and teeth and dental implants, and has been tested by orthopedic surgeons to make customized hip replacements.

Pharmaceutical rights to MIT's 3DP process are exclusively licensed to Aprecia, who developed the ZipDose® Technology platform in which products are assembled in alternating layers of powdered medication and liquid droplets without using compression forces or traditional molding techniques. As a result, products utilizing the ZipDose technology disintegrate in the mouth in approximately 10 seconds when taken with a sip of liquid. Additionally, the technology can support doses up to 1,000 mg per dose and allow for the application of enhanced taste-masking techniques.

Beyond these benefits, 3DP technology could have far-reaching implications for the pharmaceutical industry due to the potential for dose-customization where doses are individualized then printed according to the specific patient's needs. Aprecia currently has three other products in the pipeline for ZipDose technology development. Spritam is expected to be available in the first quarter of 2016 and may provide benefit for patients with epilepsy who have difficulty swallowing.

AHA/ADA Guidelines on CVD Prevention in Type 2 Diabetes

The American Heart Association (AHA) and American Diabetes Association (ADA) recently released updated joint guidelines on CVD prevention in patients with type 2 diabetes. This statement updates the 2007 guidelines and provides recommendations from the review of current literature and clinical trials related to the control of blood pressure, blood glucose and cholesterol. Emphasis is placed on lifestyle modification, including recommendations on nutrition and weight management, as well as CVD risk factor management. The updated guidelines state that hemoglobin A1c should be ≤ 7% in most patients in order to reduce the incidence of microvascular disease; however, more stringent or less stringent goals may be appropriate in select patients. The updated guidelines recommend a blood pressure goal of < 140/90 mmHg for most patients with diabetes. Additionally, pharmacological therapy should include a regimen with either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB). For CVD prevention, the AHA/ADA guidelines incorporate the AHA/American College of Cardiology 2013 recommendations that emphasize the importance of statins use based on overall CVD risk, rather than treating to a LDL-C target. The AHA/ADA statement also highlights areas where additional research is needed to further the goal of better primary CVD prevention in this population, including: the role of glucose-lowering drugs in reducing cardiovascular events, the role of bariatric surgery, the risks of hypoglycemia on the cardiovascular system, appropriate targets for blood pressure, the role of lowering triglyceride levels, and the role of imaging for subclinical CVD assessment.

The Pink Pill gets FDA Approval for Sexual Dysfunction in Women

Sexual dysfunction affects approximately 10% of women in the United States. Sprout Pharmaceuticals' flibanserin (Addyi™) was granted approval for the treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women, the most common form of female sexual dysfunction. Acquired, generalized HSDD is characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to: a co-existing medical or psychiatric condition; problems within the relationship; or the effects of a medication or other drug substance. Addyi was approved as a 100 mg pink tablet.

Flibanserin balances levels of dopamine and norepinephrine, responsible for sexual excitement, and decreases serotonin levels, which plays a role in sexual satiety/inhibition. FDA approval was based on three 24-week clinical trials that included women with an average age of 36 years and average duration of HSDD of about 5 years. On average, flibanserin 100 mg taken daily at bedtime, increased the number of satisfying sexual events by 0.5 to 1 additional event per month and improved sexual desire and distress scores both by 0.3 to 0.4 as compared to placebo. The most common side effects reported were dizziness, somnolence, and nausea.

Flibanserin is not indicated for use in men, postmenopausal women, or to enhance sexual performance. The drug label carries a boxed warning regarding concomitant use with alcohol and moderate or strong CYP3A4 enzyme inhibitors, as this may lead to severe hypotension and syncope. Flibanserin should also not be used in patients with liver impairment. Flibanserin will only be available through certified HCP and pharmacies. Market launch of flibanserin is expected by October 17, 2015. Currently, there are no FDA-approved treatments for sexual desire disorders in men.

treatment of actinic keratosis. Patients who experience throat tightness, difficulty breathing, faintness, swelling of the lips or tongue should stop using ingenol mebutate and seek immediate medical attention. The agency also received case reports of severe eye injuries and skin reactions, some of which were associated with the gel not being used according to the label instructions. Required changes to the label include information about these new safety risks and additional instructions on the safe and appropriate application of the gel.

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

- **September 4, 2015:** rolapitant; oral and intravenous (IV) neurokinin-1 (NK1) receptor antagonist, chemotherapy-induced and post-op nausea and vomiting; Tesaro/OPKO.
- **September 8, 2015:** Kanuma™; sebelipase alfa; IV lysosomal acid lipase (LAL); LAL deficiency; Synageva.
- **3rd Quarter 2015:** Aristada™; aripiprazole lauroxil; intramuscular atypical antipsychotic; schizophrenia; Alkermes.
- **3rd Quarter 2015:** Brilinta®; ticagrelor; oral platelet inhibitor; prevention of atherothrombotic events in patients post myocardial infarction; AstraZeneca.
- **3rd Quarter 2015:** Durlaza™; acetylsalicylic acid; oral NSAID; secondary prevention of stroke and acute cardiac events; New Haven.
- **2nd Half 2015:** necitumumab; IV anti-EGFR antibody; non-small cell lung cancer; Eli Lilly.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
sonidegib	Odomzo®	The FDA approved, the hedgehog pathway inhibitor, sonidegib (Odomzo) for the treatment of adults with locally advanced basal cell carcinoma (BCC). Sonidegib is indicated in patients whose BCC has recurred following surgery or radiation therapy, or who are ineligible for surgery or radiation therapy. It is approved as a 200 mg oral capsule; recommended dose is 200 mg once daily on an empty stomach. Sonidegib carries a boxed warning regarding fetal toxicities; pregnancy status should be verified prior to start of therapy; female and male patients should use appropriate contraception during and for a period after stopping therapy, as outlined in the label. Common side effects are musculoskeletal in nature and interruption or discontinuation of therapy may be required due to severity of symptoms; serum creatine kinase (CK) and creatinine levels should be monitored prior to and periodically during therapy.	Novartis	FDA NDA Approval 07/24/2015
paliperidone ER	no trade name	Paliperidone extended-release (ER) tablets, the first-time generic for Invega®, have been FDA approved. Paliperidone is an atypical antipsychotic indicated for the treatment of schizophrenia in adults and adolescents and the treatment of schizoaffective disorder in adults. Generic paliperidone ER tablets were approved as 1.5 mg, 3 mg, 6 mg, and 9 mg strengths.	Actavis	FDA aNDA Approval 08/03/2015
testosterone	no trade name	The FDA has approved testosterone topical 1.62% gel, the therapeutic equivalent of AndroGel® 1.62%. Testosterone gel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The generic testosterone 1.62% gel was approved as unit-dose packets and a metered-dose pump that delivers 20.25 mg per actuation. Testosterone gel is applied topically once daily, in the morning.	Perrigo	FDA aNDA Approval 08/04/2015
testosterone	no trade name	Testosterone 1% gel, the AB-rated generic for Fortesta®, was approved for testosterone replacement therapy for males with testosterone deficiency. Actavis' testosterone gel was approved as a 10 mg per actuation metered-dose pump, similar to brand Fortesta. The 1% gel is dosed once daily, in the morning. Generic versions of for AndroGel, Testim® and Vogelxo® 1% topical gels are also available.	Qualitest / Actavis	FDA aNDA Approval 08/05/2015
dichlorphenamide	Keveyis™	The first oral carbonic anhydrase inhibitor for the treatment of primary hyperkalemic and hypokalemic periodic paralysis and related variants, dichlorphenamide (Keveyis), has been FDA approved. Periodic paralyses are a group of rare hereditary disorders that cause episodes of muscle weakness or paralysis. Keveyis is approved as 50 mg tablets with a recommended dose of one tablet twice daily; do not exceed 200 mg per day. Patient response should be evaluated after two months of treatment to decide if therapy should be continued. Contraindications include hepatic impairment, severe pulmonary obstruction, concomitant use with high dose aspirin and hypersensitivity to dichlorphenamide or other sulfonamides. Common adverse effects include paresthesias, cognitive disorder, taste disturbance, and confusion. An increased risk of falls has been reported in older patients; dose reduction or discontinuation of the product should be considered if falls occur.	Taro	FDA NDA Approval 08/07/2015
buprenorphine/ naloxone	Zubsolv®	Orexo's buprenorphine/naloxone sublingual (SL) tablets (Zubsolv) received an expanded indication for the induction treatment of opioid dependence. The partial opioid agonist was previously only approved for the maintenance treatment of the condition. When given for induction therapy, Zubsolv is administered in divided doses and should only be initiated when objective and clear signs of withdrawal are present. Zubsolv is available as buprenorphine/naloxone SL tablets in 1.4 mg/0.36mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, and 11.4 mg/2.9 mg strengths.	Orexo	FDA sNDA Approval 08/10/2015
cysteamine bitartrate	Procysbi®	The FDA has granted an expanded indication for the cystine-depleting agent, cysteamine bitartrate (Procysbi) for use in patients 2 years of age and older with nephropathic cystinosis. Previously, the drug was only approved for use in adults and children at least 6 years of age. Procysbi is available as 25 mg and 75 mg delayed-release oral capsules. The dose is titrated to a recommended target of 1.3 g/m^2 body weight per day, regardless of age, in divided doses given every 12 hours.	Raptor	FDA sNDA Approval 08/14/2015

References
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