Magellan Rx MANAGEMENT

Clinical Alert

AUGUST 2015

Hot Topic: PCSK9 Inhibitor Spotlight

The Food and Drug Administration (FDA) has approved, alirocumab (Praluent®; Regeneron/Sanofi), the first agent in a new class of drugs to treat hyperlipidemia. Alirocumab is a **P**roprotein **C**onvertase **S**ubtilisin/**K**exin Type 9 (PSCK9) inhibitor indicated as adjunct to diet and maximally tolerated statin therapy to treat adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

HeFH is an inherited lipid disorder occurring in approximately one in 300 individuals. Cardiovascular (CV) disease continues to be a leading cause of death in American men and women, and accounts for about one out of every three deaths in the United States.

Alirocumab is self-administered subcutaneously at doses of 75 mg to 150 mg once every two weeks and is available in single-use prefilled pens and syringes. It is a monoclonal antibody that inhibits the PCSK9 protein, which acts by reducing the number of LDL receptors (LDLR) on the surface of hepatic cells that remove LDL-C from the blood. By blocking PCSK9, more receptors are available to clear LDL-C from circulation.

The FDA approval of alirocumab was based on five placebo-controlled trials that enrolled a total of 3,499 patients with HeFH, or high ASCVD risk and were on maximally tolerated doses of a statin. Significant reductions in LDL-C by approximately 40% to 60% ($p<0.0001$) have been reported for alirocumab compared with placebo. Similar reductions in non-HDL-C levels and ApoB were also observed. Additional trials that compared alirocumab with ezetimibe therapy reported a 2- to 3-fold greater reduction in LDL-C with alirocumab over ezetimibe when given with or without statins.

In general, adverse event profiles were similar between the alirocumab and placebo groups. Injection site reactions were reported in approximately 7% of patients on alirocumab. Slightly more musculoskeletal and neurocognitive adverse effects, including confusion and memory impairment, were reported with alirocumab than with placebo. Neurocognitive effects, such as transient confusion and memory loss, have been described in patients on chronic statin therapy.

As with other biologic agents, the potential exists for anti-drug antibodies to occur. Neutralizing antibodies (Nab) were identified in 1.2% of patients treated with alirocumab that lead to transient or prolonged loss of efficacy; long-term effects of alirocumab therapy in the presence of NAb are unknown.

Although, alirocumab has demonstrated significant LDL-C lowering, long-term safety and effect on CV outcomes remains unknown. The ongoing ODYSSEY OUTCOMES trial is designed to evaluate the impact of alirocumab on major CV events with results expected in 2018. In addition, safety and efficacy of alirocumab dosed every four weeks are being studied.

Statins remain the drugs of choice for lowering LDL-C and preventing CV events, including in patients with HeFH; however when target LDL-C levels are not achieved with maximally tolerated statin doses, additional therapy is needed. Alirocumab is well tolerated and has shown to significantly reduce LDL-C levels when prescribed with or without a statin.

Additional PCSK9 inhibitors for the treatment of hyperlipidemia are in the pipeline. Amgen's evolocumab (Repatha™) is expected to receive FDA approval in August 2015. Pfizer's bococizumab, which is currently being studied in phase 3 trials, could be available in 2016.

Drug Information Highlights

- California and Oregon will be the first states in the U.S. to allow pharmacists to dispense hormonal contraceptives to women without a prescription. Pharmacists must undergo additional training and perform patient health screenings prior to dispensing. In Oregon, females younger than 18 years must show proof of prior birth control prescriptions from a physician; this is not required for women 18 years and older. California has no age restrictions. California's law is anticipated to take effect after October 1, 2015, and Oregon's law after January 1, 2016.
- The FDA is evaluating potential risks of using codeine-containing cough/cold drugs in children under 18 years of age. Serious side effects, including slowed or difficult breathing are possible. Currently, the FDA advises parents and caregivers who notice signs of slow, shallow, difficult or noisy breathing, confusion or unusual drowsiness in a child taking one of these agents to stop the agent and immediately seek medical attention.
- Biogen reported the second case of progressive multifocal leukoencephalopathy (PML) associated with their oral multiple sclerosis (MS) agent, dimethyl fumarate (Tecfidera®). PML is a serious brain infection caused by the John Cunningham (JC) virus that can lead to severe disability or death in patients who are immunocompromised. Although few details are currently known, as with the first case, the patient had prolonged lymphopenia, a known risk factor for PML. Neither case resulted in death. Biogen does not anticipate any changes to the drug's label at this time, and physicians should be vigilant regarding prolonged severe lymphopenia as the label recommends. PML has also been associated with oral fingolimod (Gilenya®; Novartis) and intravenous natalizumab (Tysabri®; Biogen) used to treat MS.
- The FDA has strengthened its warning on CV risk for non-aspirin NSAIDs. Regardless of CV history, risk of heart attack and stroke increases with increased dose and duration of use; although, CV risk can be present during the first weeks of therapy. It is unknown if any one agent carries a greater risk than another. Patients taking NSAIDs should seek immediate medical attention if they experience chest pain, difficulty breathing, weakness, or slurred speech.

Contact

Dona Jones
Executive Assistant
djjones@magellanhealth.com

What's New with Hepatitis C Virus (HCV)

The FDA approved the first drugs to treat chronic HCV genotypes 3 and 4 infections as part of ribavirin-free and/or interferon-free therapies. Although, genotypes 3 and 4 account for only 10% and 1% of chronic HCV cases in the U.S., respectively, both genotypes are considered relatively difficult-to-treat infections. Both products were granted priority review.

Daclatasvir (Daklinza™; Bristol-Myers Squibb [BMS]), a NS5A inhibitor, was approved for use with sofosbuvir (Sovaldi®) for the treatment of genotype 3. In clinical studies, 12 weeks of daclatasvir plus sofosbuvir therapy provided sustained-viral response (SVR) rates of 98% in treatment-naïve and 92% in treatment-experienced patients without cirrhosis. Daclatasvir carries a Limitations of Use statement alerting prescribers of the lower SVR rates achieved in patients with cirrhosis (58% and 69%, respectively). The most common adverse reactions reported in clinical studies were headache and fatigue. Daclatasvir is available as 30 mg and 60 mg tablets.

The second product, a fixed-dose combination ombitasvir/paritaprevir/ritonavir (Technivie™; AbbVie) was approved for use with ribavirin for the treatment of HCV genotype 4 infections in patients with no cirrhosis. SVR rates of 100% and 91% were reported with Technivie when given with and without ribavirin, respectively. Fatigue, weakness, nausea, insomnia, and itching were reported when prescribed with ribavirin. The drugs in Technivie are similar to those in the combination product, Viekira Pak™, minus dasabuvir, which is not effective against genotype 4. Launch of the product is expected in mid to late August, 2015.

Sofosbuvir, given with ribavirin, was previously the only oral agent FDA approved to treat HCV genotypes 3 and 4; although, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) also recommend off-label uses of ledipasvir/sofosbuvir (Harvoni™) or ombitasvir/paritaprevir/ritonavir (Viekira Pak minus dasabuvir) plus ribavirin for 12 weeks in treatment-naïve patients with genotype 4.

Additional news surrounding HCV includes an update to the AASLD/IDSA HCV treatment guidelines. Revisions were made to the sections on When and In Whom to Initiate Therapy, Initial Treatment, Retreatment, Acute HCV Infection, and Unique Populations. AASLD/IDSA emphasize that all patients with chronic HCV be treated, with the exception of those with short life expectancies due to comorbid conditions. Priority for immediate treatment should be given to patients at risk for liver-related complications, based on available resources. AASLD/IDSA strengthened its recommendation on the use of sofosbuvir plus simeprevir for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without Q80K polymorphism) in treatment-naïve patients with genotype 1a or 1b. Patients with genotype 1a or 1b without cirrhosis who have failed peginterferon/ribavirin treatment should receive daily sofosbuvir plus simeprevir for 12 weeks. Treatment-naive patients with HCV genotype 3 should receive sofosbuvir plus ribavirin plus peginterferon for 12 weeks or, alternatively, sofosbuvir and ribavirin for 24 weeks if they are interferon-eligible; daclatasvir was not available in the U.S. at the time of this update. For treatment-naïve patients with genotypes 5, AASLD/IDSA recommends off-label use of ledipasvir/sofosbuvir for 12 weeks as the preferred therapy. For further details, please visit the complete guidelines at www.aasld.org.

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

- **August 22, 2015:** aripiprazole lauroxil; intramuscular (IM) 5-HT1A and D2 partial agonist, 5-HT2A partial antagonist; schizophrenia; Alkermes.
- **August 27, 2015:** Optivo®; nivolumab; intravenous (IV) anti-PD1 antibody; advanced melanoma, squamous cell carcinoma, metastatic kidney cancer, gastric cancer; recurrent/metastatic head and neck cancer; BMS/Ono.
- **August 2015:** empagliflozin/metformin; oral SGLT2 inhibitor/biguanide; T2DM; Boehringer Ingelheim.
- **August 2015:** asfotase alfa; subcutaneous alkaline phosphate enzyme; hypophosphatasia; Alexion.
- **August 2015:** Yondelis®; trabectedin; IV alkylating agent; soft tissue sarcoma, ovarian cancer; Janssen/PharmaMar.
- **August 2015:** Addyi™; flibanserin; oral 5-HT1A partial agonist, 5-HT2A agonist; female sexual dysfunction; Sprout.
- **August 2015:** Remsima™; infliximab; injectable TNF-alpha inhibitor; rheumatoid arthritis; Hopsira/Celltrion
- **3rd Quarter 2015:** Brilinta®; ticagrelor; oral platelet inhibitor; prevention of atherothrombotic events in patients post MI; AstraZeneca.
- **3rd Quarter 2015:** Durlaza™; acetylsalicylic acid; oral NSAID; secondary prevention of stroke and acute cardiac events; New Haven.
- **2nd Half 2015:** necitumumab; anti-EGFR antibody; non-small cell lung cancer; Eli Lilly.

ASCO Guidelines for the Use of White Blood Cell (WBC) Growth Factors

The American Society of Clinical Oncology (ASCO) published an update to its 2006 clinical practice guidelines on the use of white blood cell (WBC) growth factors (a.k.a hematopoietic colony-stimulating factors [CSF]). Changes include the addition of biosimilar agents, moderation of the recommendation around routine use of CSFs in older patients with diffuse aggressive lymphoma, and new recommendations against routine dose-dense chemotherapy in lymphoma and in favor of high-dose-intensity chemotherapy for urothelial cancer. Key revisions include:

- Primary prophylaxis with a CSF starting with the first cycle and all subsequent cycles of chemotherapy is recommended in patients who have approximately 20% or higher risk for febrile neutropenia based on patient-, disease-, and treatment-related factors. Whenever possible, physicians should consider prescribing alternative chemotherapy regimens that are equally safe and effective and do not require CSF support.
- Efficacy data support the use of CSFs with dose-dense chemotherapy for the adjuvant treatment of high-risk breast cancer, and with high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer. Dose-dense chemotherapy regimens with CSF support should only be used within an appropriately designed clinical trial or if supported by credible efficacy data.
- Pegfilgrastim, filgrastim, and the biosimilar products tbo-filgrastim, and filgrastim-sndz (Zarxio™) can be used for the prevention of treatment-related febrile neutropenia. Zarxio is expected on the market as of September 2, 2015. Other CSF biosimilar products may be included in the guidance as they become available.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
lumacaftor / ivacaftor	Orkambi™	The FDA has approved Orkambi, a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) potentiator which is a combination of lumacaftor and ivacaftor for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the CFTR gene. Safety and efficacy have not been established in patients with CF who are not homozygous for the *F508del* mutation. It is available as an oral tablet containing lumacaftor 200 mg and ivacaftor 125 mg with a recommended dose of two tablets orally every 12 hours with fat-containing food. Orkambi received FDA's breakthrough therapy designation and was granted orphan drug status.	Vertex	FDA NDA Priority Approval 07/02/2015
sacubitril / valsartan	Entresto™	Entresto, a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB), has been approved by the FDA to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction. Entresto should be administered in conjunction with other HF therapies, in place of an ACE inhibitor or another ARB. Entresto is dosed orally twice daily and is available in the following sacubitril/valsartan tablet strengths: 24/26 mg, 49/51 mg and 97/103 mg. As with other drugs that act directly on the renin-angiotensin system, Entresto carries a boxed warning for fetal toxicity.	Novartis	FDA NDA Approval 07/07/2015
brexpiprazole	Rexulti®	The FDA approved the atypical antipsychotic brexpiprazole (Rexulti) for the treatment of schizophrenia and for use as an adjunct to antidepressants for the treatment of major depressive disorder (MDD) in adults. Following a titration period, brexpiprazole is taken orally once daily with 2 mg/day recommended for MDD and 2 to 4 mg/day recommended for schizophrenia. It is available as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets. Brexpiprazole carries the same boxed warnings regarding dementia-related psychosis as other atypical antipsychotics as well as a warning for increased risk of suicidal thoughts in young patients taking antidepressants. Safety and efficacy of brexpiprazole have not been established in pediatric patients.	Otsuka	FDA NDA Approval 07/10/2015
tacrolimus extended release	Envarsus XR®	The immunosuppressant, tacrolimus (Envarsus XR), was FDA approved for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release (IR) formulations in combination with other immunosuppressants. Envarsus XR is available as extended-release (ER) 0.75 mg, 1 mg, and 4 mg tablets and is not interchangeable or substitutable with other tacrolimus products. Patients converting from tacrolimus IR should receive 80% of the pre-conversion daily dose of tacrolimus IR with a tacrolimus ER target whole blood trough concentration of 4 to 11 ng/mL. Tacrolimus and other immunosuppressants carry a boxed warning regarding increased risk for the development of serious infections and malignancies.	Veloxis	FDA NDA Approval 07/10/2015
gefitinib	Iressa®	The FDA granted orphan drug designation for the EGFR tyrosine inhibitor, gefitinib (Iressa) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test. Gefitinib, available in a 250 mg oral tablet,is dosed once daily. The therascreen® EGFR RGQ PCR Kit (by Qiagen) has been FDA-approved as a companion test for gefitinib. Gefitinib originally received accelerated approval in 2003 for advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel; however, it was voluntarily withdrawn after confirmatory trials did not show a clinical benefit.	AstraZeneca	FDA NDA Approval 07/13/2015
adapalene / benzoyl peroxide	Epiduo® Forte	Epiduo Forte, a combination of the retinoid, adapalene 0.3%, and benzoyl peroxide 2.5%, was FDA approved for the topical treatment of acne vulgaris. Safety and efficacy has not been established in patients less than 12 years of age. It is to be applied to affected areas of the face and/or trunk once daily after washing. It is available as a gel in 15 g, 30 g, 45 g, 60 g and 70 g pumps. Epiduo® containing adapalene 0.1%/benzoyl peroxide 2.5% is already available, and is indicated for treatment of acne vulgaris in patients nine years of age and older.	Galderma	FDA NDA Approval 07/15/2015

References
https://www.magellanmedicaid.com/news/clinicalalerts.asp
www.aasld.org
www.asco.org
www.cdc.gov
www.fda.gov
www.medscape.com
www.pubmed.gov