Pharmaceutical Approval Update

Kunj Gohil, PharmD, RPh

Alirocumab Injection (Praluent)

Manufacturer: Sanofi-Aventis U.S., Bridgewater, New Jersey, and Regeneron Pharmaceuticals Inc., Tarrytown, New York

Date of Approval: July 24, 2015

Indication: Praluent is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein-cholesterol (LDL-C).

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Drug Class: Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor

Uniqueness of Drug: Alirocumab is a human monoclonal antibody that binds to PCSK9. PCSK9 binds to low-density lipoprotein receptors (LDLR) on the surface of hepatocytes and promotes LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL-C; therefore, a decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDl-C, resulting in lower LDL-C levels.

Warnings and Precautions:

Allergic reactions. If signs or symptoms of serious allergic reactions occur, discontinue treatment, treat according to the standard of care, and monitor until signs and symptoms resolve.

Dosage and Administration: The recommended starting dose is 75 mg administered subcutaneously once every two weeks. If the response is inadequate, the dosage may be increased to a maximum of 150 mg administered every two weeks.

Commentary: Praluent was the first LDL-C–lowering medication approved in the highly anticipated class of PCSK9 inhibitors, which represent a novel way to reduce LDL-C in specific patient populations. Data from clinical trials showed significant LDL-C–lowering ability for Praluent, but further evidence is required to determine the potential for a reduction in cardiovascular risk. Concern exists about the pricing of this new biologic, as it has an estimated annual wholesale acquisition cost of $14,600.

Sources: www.fda.gov, Praluent prescribing information

Flibanserin (Addyi)

Manufacturer: Sprout Pharmaceuticals, Raleigh, North Carolina

Date of Approval: August 18, 2015

Indication: Addyi is indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), 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 in the relationship.
- The effects of a medication or other drug substance.

Drug Class: Addyi is a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist.

Uniqueness of Drug: The mechanism of action of flibanserin in the treatment of premenopausal women with HSDD is not known.

Warnings and Precautions:

Hypotension and syncope due to an interaction with alcohol. Alcohol use is contraindicated in patients taking flibanserin. Before prescribing flibanserin, the health care provider must assess the likelihood of the patient abstaining from alcohol use, taking into account the patient's current and past drinking behavior and other pertinent social and medical history. Counsel patients who are prescribed flibanserin about the importance of abstaining from alcohol use.

Addyi REMS Program. Flibanserin is available only under the restrictions of a risk evaluation and mitigation strategy (REMS) called the Addyi REMS Program because of the increased risk of severe hypotension and syncope related to the interaction between flibanserin and alcohol (as described in the boxed warning and the warnings and precautions section of the label). Notable requirements of the Addyi REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Pharmacies must be certified with the program and must only dispense to patients pursuant to a prescription from a certified prescriber.

Hypotension and syncope with cytochrome P450 (CYP 450) 3A4 inhibitors. The concomitant use of flibanserin with moderate or strong CYP3A4 inhibitors significantly increases flibanserin concentrations, which can lead to hypotension and syncope. Concomitant use of multiple weak CYP3A4 inhibitors that may include herbal supplements (e.g., ginkgo, resveratrol) or nonprescription drugs (e.g., cimetidine) could also lead to clinically relevant increases in flibanserin concentrations that may increase the risk of hypotension and syncope.

Central nervous system (CNS) depression. The risk of CNS depression is increased if flibanserin is taken during waking hours, if flibanserin is taken with alcohol or other CNS depressants, or if flibanserin is taken with medications that increase flibanserin concentrations, such as CYP3A4 inhibitors.

Hypotension and syncope with flibanserin alone. Consider the benefits of flibanserin and the risks of hypotension and syncope in patients with pre-existing conditions that predispose them to hypotension. Patients who experience presyncope should immediately lie supine and promptly seek medical help if the symptoms do not resolve. Prompt medical attention should also be obtained for patients who experience syncope.

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Syncope and hypotension in patients with hepatic impairment. The use of flibanserin is contraindicated in patients with hepatic impairment.

Mammary tumors in female mice. The clinical significance of these tumors is unknown

Dosage and Administration: The recommended dosage of flibanserin is 100 mg administered orally once daily at bedtime.

Commentary: Addyi is the first agent approved by the Food and Drug Administration for sexual desire disorder in women. Due to the severity of adverse events associated with Addyi and alcohol use, such as hypotension and syncope, the drug is approved with a REMS. This program requires prescribers to be certified and mandates counseling about the risk of severe hypotension and syncope and about the importance of not drinking during treatment.

Sources: www.fda.gov, Addyi prescribing information

Daclatasvir (Daklinza)

Manufacturer: Bristol-Myers Squibb, Princeton, New Jersey

Date of Approval: July 24, 2015

Indication: Daklinza is indicated for use with sofosbuvir (Sovaldi, Gilead Sciences) for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection.

Drug Class: Daklinza is a direct-acting antiviral (DAA) agent against HCV.

Uniqueness of Drug: This DAA is an inhibitor of NS5A, a nonstructural protein encoded by HCV; it binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.

Warnings and Precautions:

Risk of adverse reactions or loss of virological response due to drug interactions. The concomitant use of daclatasvir and other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of daclatasvir and possible development of resistance.
- Dosage adjustments of concomitant medications or daclatasvir.
- Possible clinically significant adverse reactions from greater exposure to concomitant drugs or daclatasvir.

Serious symptomatic bradycardia when coadministered with sofosbuvir and amiodarone. Coadministration of amiodarone with daclatasvir in combination with sofosbuvir is not recommended. For patients taking amiodarone who have no alternative treatment options and who will be coadministered daclatasvir and sofosbuvir:

- Counsel patients about the risk of serious symptomatic bradycardia.
- Cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first two weeks of treatment.

Dosage and Administration: The recommended dosage of daclatasvir is 60 mg, taken orally once daily in combination with sofosbuvir for 12 weeks. Daclatasvir may be taken with or without food.

Commentary: The Centers for Disease Control and Prevention estimates that 10% of the 2.7 million patients with HCV have genotype 3. This therapy provides patients who cannot tolerate ribavirin with a new option for the treatment of HCV genotype 3. Clinical trials demonstrated a significant sustained virological response in both treatment-naïve and treatment-experienced patients.

Sources: www.fda.gov, Daklinza prescribing information

Ombitasvir/Paritaprevir/Ritonavir (Technivie)

Manufacturer: AbbVie Inc., North Chicago, Illinois

Date of Approval: July 24, 2015

Indication: Technivie is indicated in combination with ribavirin for the treatment of patients with chronic hepatitis C virus (HCV) genotype 4 infection without cirrhosis.

Drug Class: Technivie is a fixed-dose combination tablet containing an HCV NS5A inhibitor (ombitasvir), an HCV NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A-mediated metabolism of paritaprevir, thereby providing an increased plasma concentration of paritaprevir.

Uniqueness of Drug: Technivie combines two DAA agents with distinct mechanisms of action and nonoverlapping resistance profiles to target HCV at multiple steps in the viral lifecycle:

- Ombitasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of ombitasvir has been characterized based on cell-culture antiviral activity and drug-resistance mapping studies.
- Paritaprevir is an inhibitor of HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV-encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

Warnings and Precautions:

Increased risk of alanine transaminase (ALT) elevations. Hepatic laboratory testing should be performed during the first four weeks of treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely. Patients should be instructed to consult their health care professional without delay if they experience the onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces. Consider discontinuing the drug if ALT levels remain persistently greater than 10 times the upper limit of normal. Discontinue the drug if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio.

Risks associated with ribavirin combination treatment. The warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen.

Risk of adverse reactions or reduced therapeutic effect due to drug interactions. The concomitant use of this drug

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and certain other drugs may result in known or potentially significant drug interactions. Consider the potential for drug interactions prior to and during Technivie therapy; review concomitant medications during Technivie therapy; and monitor for the adverse reactions associated with the concomitant drugs.

Risk of human immunodeficiency virus (HIV)-1 protease inhibitor drug resistance in HCV/HIV-1 coinfected patients. The ritonavir component of this product is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 coinfected patients treated with this drug should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

Dosage and Administration: The recommended dosage of this fixed-dose combination tablet of ombitasvir, paritaprevir, and ritonavir is two tablets taken orally once daily (in the morning).

Commentary: Genotype 4 is one of the least common HCV genotypes. This therapy provides patients who cannot tolerate interferon with a new option to manage their HCV genotype 4. Results from clinical trials were very promising, as a sustained virological response (SVR) of 100% was seen when Technivie was administered with ribavirin; a 91% SVR resulted when it was used without ribavirin.

Sources: www.fda.gov, Technivie prescribing information ■