Alirocumab (Praluent): First in the New Class of PCSK9 Inhibitors
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INTRODUCTION

Hyperlipidemia, also known as hypercholesterolemia, is characterized by elevated cholesterol levels in the blood and is a leading cause of atherosclerosis, coronary heart disease, stroke, and peripheral vascular disease. These conditions account for approximately one-third of all deaths in middle-aged and older adults in the U.S., and their incidence is likely to increase as a result of the obesity epidemic. The two main factors causing hyperlipidemia worldwide are lifestyle and genetic predisposition.

Cholesterol, a fat-like substance produced by the liver, is necessary for a variety of bodily functions, including building cell membranes, producing hormones, and aiding in the digestion of fat. The two major types of cholesterol are low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C). Elevated levels of LDL-C lead to atherosclerosis—the buildup of fatty deposits in the arteries. These deposits, in turn, can cause narrowing of the blood vessels and reduce blood flow to the heart and brain, resulting in an increased risk of heart attack and stroke. HDL-C is believed to be protective against heart attack and stroke because of its ability to remove cholesterol from the arteries and return it to the liver.

The 2013 American College of Cardiology/American Heart Association (AHA) guidelines on the assessment of cardiovascular risk provide recommendations for estimating cardiovascular disease risk. The atherosclerotic cardiovascular disease (ASCVD) risk calculator takes into account a patient’s gender, race, age, cholesterol levels, blood pressure levels, use of blood pressure medications, diabetes, and smoking status. This tool allows health care providers to estimate a patient’s 10-year and lifetime risks for ASCVD.

The main goal of lipid-lowering therapy is to reduce a patient’s risk of cardiovascular disease and stroke. A 2013 Cochrane review showed that statins reduce all-cause mortality, composite cardiovascular disease endpoints, fatal and nonfatal CVD events, total and LDL cholesterol, and revascularization. Current AHA guidelines focus on matching a patient’s risk level with the intensity of statin treatment. The ACC/AHA recommendations identified four “statin benefit” groups in which the potential for an ASCVD risk reduction exceeds the potential for adverse effects: 1) patients with clinical ASCVD; 2) patients with primary elevations in LDL-C greater than or equal to 190 mg/dL; 3) patients 40 to 75 years of age with diabetes and LDL-C levels of 70 to 189 mg/dL; and 4) patients 40 to 75 years of age with LDL-C levels of 70 to 189 mg/dL and an estimated 10-year ASCVD risk greater than or equal to 7.5%.

Statin therapy has been the most efficient pharmacological treatment option for hyperlipidemia. Statins have been shown to decrease LDL-C levels, and, at higher doses, some have reduced triglyceride levels while increasing HDL-C levels. Although statins are generally well tolerated, not all hyperlipidemic patients are candidates for statin therapy. Intolerance to treatment can occur because of undesirable side effects, such as myalgia and, in more severe cases, rhabdomyolysis. Statins are substrates of cytochrome P450 (CYP) 3A4. The risk of rhabdomyolysis increases significantly when a CYP3A4 inhibitor is coadministered with a statin.

In July 2015, the FDA approved alirocumab injection (Praluent, Regeneron/Sanofi), the first cholesterol-lowering treatment in a new class of drugs known as proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors. Alirocumab was approved for use as an adjunct to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD, such as heart attacks or strokes, who require additional LDL-C lowering. One month later, in August 2015, the FDA approved a second PCSK9 inhibitor, evolocumab (Repatha, Amgen), for patients with HeFH or ASCVD, as well as for those with homozgyous familial hypercholesterolemia (HoFH), who are unable to control their LDL-C levels.

In this article, we review the clinical features of alirocumab.

DESCRIPTION

Alirocumab is a human monoclonal antibody (an immunoglobulin G1 [IgG1] isotype) that inhibits PCSK9. It is produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture.

Alirocumab consists of two disul-
fide-linked human heavy chains, each covalently linked through a disulfide bond to a kappa light chain. A single N-linked glycosylation site is located in each heavy chain within the CH2 domain of the Fc constant region of the molecule. The variable domains of the heavy and light chains combine to form the PCSK9 binding site within the antibody. The molecular weight is approximately 146 kDa.9

**MECHANISM OF ACTION**

Low-density lipoprotein receptors (LDLRs) are the primary receptors that clear circulating LDL-C. PCSK9 binds to LDLRs on the surface of hepatocytes, promoting LDLR degradation in the liver and, in turn, elevating LDL-C blood levels. By inhibiting the binding of PCSK9 to LDLR, alirocumab reduces LDL-C levels.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

After a single subcutaneous (SC) dose of alirocumab (75 mg or 150 mg), maximal inhibition of free PCSK9 occurs within four to eight hours in a concentration-dependent manner. The median apparent half-life at steady state is 17 to 20 days in patients who receive alirocumab SC (75 mg or 150 mg every two weeks).

**Pharmacokinetics**

**Absorption**

The maximum serum concentration (C_{max}) of alirocumab is achieved within three to seven days after SC administration of 75 mg or 150 mg. Steady state is reached after two or three doses, with an accumulation ratio of approximately twofold. The absolute bioavailability of alirocumab is approximately 85%.

**Distribution**

After intravenous administration, alirocumab has a volume of distribution of approximately 0.04 to 0.05 L/kg.

**Metabolism**

Since alirocumab is a protein, specific metabolism studies were not conducted. The drug is expected to degrade to small peptides and individual amino acids. Alirocumab has no affect on CYP enzymes or transporter proteins, such as permeability glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP).

**Elimination**

At low concentrations, the elimination of alirocumab occurs predominately via saturable binding to PCSK9. At higher concentrations, elimination is through a nonsaturable proteolytic pathway.

**INDICATION**

Alirocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for adults with HeFH or clinical ASCVD who are in need of additional lowering of LDL-C.

**SAFETY PROFILE**

**Contraindication**

Alirocumab is contraindicated in patients with a history of serious hypersensitivity reactions to alirocumab.

**Warnings and Precautions**

Hypersensitivity reactions, including serious events such as hypersensitivity vasculitis and hypersensitivity requiring hospitalization, have been reported with the use of alirocumab.

The effects of alirocumab on cardiovascular morbidity and mortality have not been determined.

**Adverse Events**

The safety of alirocumab was evaluated in nine placebo-controlled trials involving a total of 2,476 patients receiving active treatment. The adverse events most commonly observed in these studies included nasopharyngitis (11.3%), injection-site reactions (7.2%), influenza (5.7%), and urinary tract infections (4.8%) (Table 1).

**Special Populations**

**Pregnancy**

No data are available on the use of alirocumab in pregnancy. Animal reproduction studies have shown that alirocumab crosses the placental barrier, as do other IgG antibodies. The benefits and risks of treatment should be considered before alirocumab is used in pregnant women. There is no information on the presence of alirocumab in human milk, on the drug’s effects in breastfed infants, or on the drug’s effects on lactation.

**Pediatric and Geriatric Use**

The safety and efficacy of alirocumab have not been established in pediatric patients. No overall differences in the safety and efficacy of alirocumab were observed in patients 65 years of age and older versus younger patients, but greater sensitivity of older individuals to alirocumab cannot be ruled out.

**Renal or Hepatic Impairment**

No dose adjustments are needed for patients with mild or moderate renal or hepatic impairment. No data are available in patients with severe renal or hepatic impairment.

**DRUG–DRUG INTERACTIONS**

The median apparent half-life of alirocumab is reduced to 12 days when it is administered with a statin. This difference is not clinically meaningful and does not affect dosing recommendations.

**PIVOTAL CLINICAL STUDIES**

The efficacy of alirocumab was evaluated in a global clinical trial program (ODYSSEY) consisting of five double-blind, placebo-controlled studies. All of these studies had the percent change in LDL-C from baseline at week 24 as their primary efficacy endpoints.

**ODYSSEY LONG TERM Trial**

The ODYSSEY LONG TERM trial was a phase 3, double-blind, placebo-controlled study involving 2,341 patients...
with HeFH and/or ASCVD. All of the subjects had an LDL-C level of 70 mg/dL or greater and were receiving maximally tolerated statin doses. The subjects were randomly assigned to receive alirocumab 150 mg or placebo as a 1-mL SC auto-injection every two weeks for 78 weeks. The study’s primary endpoint was the percent change in LDL-C from baseline at week 24.

A total of 2,310 patients were included in the intent-to-treat cohort. At week 24, the difference between the alirocumab and placebo groups in the mean percentage-point change from baseline in calculated LDL-C was −62 (−61.0% versus −0.8%, respectively; P < 0.001); this treatment effect remained consistent over 78 weeks. The mean absolute LDL-C levels for alirocumab and placebo at week 24 were 48 mg/dL and 119 mg/dL, respectively, corresponding to a mean absolute change from baseline of −74 mg/dL and −4 mg/dL.

The alirocumab group, compared with the placebo group, had higher rates of injection-site reactions (5.9% versus 4.2%, respectively), myalgia (5.4% versus 2.9%), neurocognitive events (1.2% versus 0.5%), and ophthalmologic events (2.9% versus 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (i.e., death from coronary heart disease, nonfatal myocardial infarction [MI], fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was significantly lower with alirocumab than with placebo (1.7% versus 3.3%, respectively; nominal P = 0.02).

**ODYSSEY COMBO I Trial**

The ODYSSEY COMBO I trial was a 52-week, phase 3, double-blind, placebo-controlled study involving 316 patients with hypercholesterolemia who were receiving maximally tolerated statin doses, with or without other lipid-lowering therapy, but who required additional LDL-C reduction. The patients were initially assigned to receive self-injected SC alirocumab 75 mg or placebo every two weeks. At week 12, the alirocumab dosage was increased to 150 mg every two weeks if the patient’s LDL-C level was greater than or equal to 70 mg/dL at week 8.

The study’s primary endpoint was the percent change in LDL-C from baseline at week 24. At this time point, the estimated mean changes in LDL-C from baseline were −48.2% and −2.3% for alirocumab and placebo, respectively, representing a mean difference of −45.9 percentage points (P < 0.0001). LDL-C levels of less than 70 mg/dL were achieved by 75% of alirocumab-treated patients compared with 9% of placebo patients by week 24 (P < 0.001).

**ODYSSEY FH I and FH II Trials**

ODYSSEY FH I and FH II were 78-week, phase 3, double-blind, placebo-controlled studies involving a total of 735 patients with HeFH who were receiving maximally tolerated statin doses, with or without other lipid-lowering therapy, but who required additional LDL-C reduction. The two studies were similar in regard to design and eligibility. The patients initially received either self-injected alirocumab 75 mg or placebo every two weeks. At week 12, the alirocumab dosage was increased to 150 mg every two weeks if the patient’s LDL-C level was greater than or equal to 70 mg/dL at week 8. Both studies had a duration of 78 weeks.

Mean LDL-C levels decreased from 144.7 mg/dL at baseline to 71.3 mg/dL (−57.9 percentage points versus placebo) at week 24 among alirocumab-treated patients in the FH I trial and from 134.6 mg/dL to 67.7 mg/dL (−51.4 percentage points versus placebo) in the FH II study (P < 0.0001). These reductions were maintained through week 78. LDL-C levels of less than 70 mg/dL (regardless of cardiovascular risk) were achieved at week 24 by 59.8% and 68.2% of alirocumab-treated patients in the FH I and FH II trials, respectively.

**ODYSSEY HIGH FH Trial**

The ODYSSEY HIGH FH trial was a phase 3, double-blind, placebo-controlled study involving 106 patients with HeFH receiving maximally tolerated statin doses, with or without other lipid-lowering therapy, who required additional LDL-C reduction. All of the patients had LDL-C levels greater than or equal to 160 mg/dL. The patients were randomly assigned to receive alirocumab 150 mg (n = 71) or placebo (n = 35) every two weeks via a 1-mL SC auto-injection for 78 weeks. The trial’s primary endpoint was the percent change in LDL-C levels from baseline to week 24.

Significant reductions in LDL-C from baseline at week 24 were observed with alirocumab compared with placebo. The mean percent change from baseline in LDL-C in the alirocumab-treated group was −45.7% compared with −6.6% for the placebo group, for a treatment difference of −39.1 percentage points (P < 0.0001). At week 24, the LDL-C goal was reached by 41.0% of the alirocumab group compared with 5.7% of the placebo group (P = 0.0016).

**ODYSSEY OUTCOMES Trial**

In addition to the five completed ODYSSEY studies, a new phase 3, placebo-controlled trial, ODYSSEY OUTCOMES, is under way in approximately 18,000 patients with a recent acute coronary syndrome (ACS): acute MI or unstable angina. The study’s primary objective is to evaluate whether alirocumab (75 mg or 150 mg by SC injection every two weeks), initiated one to 12 months after an index ACS event, reduces the incidence of the composite outcome of coronary heart disease death, major nonfatal coronary events (MI or hospitalization for unstable angina), or ischemic stroke. The study began in October 2012 and is scheduled for completion in December 2017.

**DOSAGE AND ADMINISTRATION**

The recommended starting dosage of alirocumab is 75 mg SC once every two weeks. If the patient’s LDL-C response is inadequate, the dosage may be increased to a maximum of 150 mg SC every two weeks.

**STORAGE AND HANDLING**

The prefilled syringes and pens should be stored in a refrigerator at 36° F to 46° F (2° C to 8° C) in the outer carton to protect them from light. The syringes and pens should be allowed to warm to room temperature for 30 to 40 minutes before use. Alirocumab should be used as soon as possible after it has warmed up. The time out of refrigeration should not exceed 24 hours at 77° F. The syringe and pens must not be reused, and they should be disposed of in a puncture-resistant container.

**PATIENT COUNSELING: PRODUCT USE**

Since alirocumab is administered via SC auto-injection, patients and/or their caregivers should be educated on the proper use of the product. Directions for
in the injection area with an alcohol wipe.
- **Step 3:** Pull off the needle cap.
- **Step 4:** Pinch a fold of skin at the injection site.
- **Step 5:** Insert the needle into the fold of skin with a quick dart-like motion.
- **Step 6:** Push the plunger down slowly and steadily.
- **Step 7:** Check that the syringe is empty before removing the needle.
- **Step 8:** Discard the syringe and cap in a puncture-resistant container.

Directions for using the prefilled pen (Figure 2) are as follows:

- **Step 1:** Look at the window on the pen and make sure that the liquid is clear, colorless to pale yellow, and free from particles.
- **Step 2:** Let the pen warm to room temperature for 30 to 40 minutes.
- **Step 3:** Wash the hands with soap and water, and then clean the skin in the injection area with an alcohol wipe.
- **Step 4:** Pull off the blue cap.
- **Step 5:** Press the yellow safety cover onto the skin at a 90-degree angle until the yellow safety cover is no longer visible.
- **Step 6:** Push and immediately release the green button; keep holding the pen against the skin. When a click is heard, the injection has started. The injection may take up to 20 seconds.
- **Step 7:** Check that the window has turned yellow before removing the pen. (A second click will be heard.)
- **Step 8:** Discard the pen and cap in a puncture-resistant container.

Patients may inject alirocumab into the thighs, stomach, or upper arms. The injection site should be rotated each time the patient takes an injection.9

**P&T CONSIDERATIONS**

**Alirocumab Versus Evolocumab**

Alirocumab and its competitor evolocumab are similar in terms of their chemical makeup, mechanism of action, and other features (Table 2). Both are human monoclonal antibodies that target PCSK9. Alirocumab, however, is an IgG1 isotype, whereas evolocumab is an IgG2 isotype. Both products are supplied as prefilled syringes and auto-injectors, and both have similar pharmacological profiles, precautions, and adverse events. Further, both products have similar average wholesale prices (AWPs), as discussed below.

The treatments differ, however, in two ways that favor evolocumab. First, alirocumab is indicated only for patients with HeFH or ASCVD, whereas evolocumab is also used in patients with HoFH. Moreover, alirocumab must be administered once every two weeks in patients with HeFH or ASCVD, whereas evolocumab can also be used once monthly (at a dose of 420 mg), which may promote better compliance.3,20

**Cost**

Alirocumab is available in cartons containing one or two prefilled syringes or prefilled pens in two strengths: 75 mg and 150 mg. The cost of alirocumab is the same for the syringes and pens at both dosage strengths.20 Table 3 shows current wholesale pricing for alirocumab and evolocumab.

**CONCLUSION**

Alirocumab was the first agent in the new class of PCSK9 inhibitors to be approved for clinical use. It is indicated as an adjunct to diet and maximally tolerated statin therapy in adults with HeFH or clinical ASCVD who require additional LDL-C lowering. The approval of alirocumab provides another treatment option for patients who have been unable to control their LDL-C levels with statin therapy.

**REFERENCES**

Table 2  Key Features of the PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Features</th>
<th>Alirocumab (Praluent)</th>
<th>Evolocumab (Repatha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>PCSK9 inhibitor antibody (IgG1)</td>
<td>PCSK9 inhibitor antibody (IgG2)</td>
</tr>
<tr>
<td>Indications</td>
<td>• HeFH • ASCVD</td>
<td>• HeFH • HoFH • ASCVD</td>
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<tr>
<td>Dosage strengths</td>
<td>• 75 mg • 150 mg</td>
<td>• 140 mg • 420 mg (using three 140-mg injections)</td>
</tr>
<tr>
<td>How supplied</td>
<td>• Prefilled syringe</td>
<td>• Prefilled syringe</td>
</tr>
<tr>
<td></td>
<td>• Prefilled auto-injector</td>
<td>• Prefilled auto-injector</td>
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<tr>
<td>Administration</td>
<td>SC once every 2 weeks</td>
<td>SC once every 2 weeks or once monthly</td>
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<tr>
<td>Time to maximum</td>
<td>4 to 8 hours</td>
<td>4 hours</td>
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<tr>
<td>suppression of unbound</td>
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<td></td>
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<tr>
<td>PCSK9</td>
<td>3 to 7 days</td>
<td>3 to 4 days</td>
</tr>
<tr>
<td>Time to maximum serum</td>
<td>17 to 20 days</td>
<td>11 to 17 days</td>
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<tr>
<td>concentration</td>
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<tr>
<td>Bioavailability</td>
<td>Approximately 85%</td>
<td>72%</td>
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<tr>
<td>Half-life</td>
<td>420 mg (using three 140-mg injections)</td>
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<tr>
<td></td>
<td>140 mg/mL prefilled syringe or auto-injector (pen)</td>
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</tr>
<tr>
<td></td>
<td>150 mg/mL prefilled syringe or auto-injector (pen)</td>
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<td>Warnings and precautions</td>
<td>Allergic reactions</td>
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<td>Common adverse events</td>
<td>• Nasopharyngitis</td>
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<td>• Injection-site reactions</td>
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<td></td>
<td>• Influenza</td>
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<td></td>
<td>• Upper respiratory tract infections</td>
<td>• Back pain</td>
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<tr>
<td>Effect on cardiovascular</td>
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<tr>
<td>morbidity/mortality</td>
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| ASCVD                    | atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IgG = immunoglobulin G; PCSK9 = proprotein convertase subtilisin kexin type 9; SC = subcutaneous.

Table 3  Cost Comparison of the PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>PCSK9 Inhibitor</th>
<th>AWP (per Unit)*</th>
<th>AWP (30-Day Supply)*</th>
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<tbody>
<tr>
<td>Alirocumab (Praluent)</td>
<td></td>
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<tr>
<td>75-mg/mL prefilled syringe or auto-injector (pen)</td>
<td>$672</td>
<td>$1,344</td>
</tr>
<tr>
<td>150-mg/mL prefilled syringe or auto-injector (pen)</td>
<td>$672</td>
<td>$1,344</td>
</tr>
<tr>
<td>Evolocumab (Repatha)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>140-mg/mL prefilled syringe or auto-injector</td>
<td>$651</td>
<td>For primary hyperlipidemia with ASCVD or for HeFH: 140 mg every two weeks, $1,302; or 420 mg once a month, $1,953 For HoFH: 420 mg once a month, $1,953</td>
</tr>
</tbody>
</table>

* As of December 2015, rounded to the nearest dollar.

ASCVD = atherosclerotic cardiovascular disease; AWP = average wholesale price; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; PCSK 9 = proprotein convertase subtilisin kexin type 9.

15. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the


