New Drug Overview
Praluent® (alirocumab)

- **Overview/Summary:** Praluent® (alirocumab) is Food and Drug Administration (FDA)-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte LDL receptors and increased LDL-C levels. Alirocumab works to inhibit the action of this enzyme leading to a decrease in LDL-C levels. 1

  Although the agent has demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, the agent was only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1]

  Currently available consensus treatment guidelines do not address the place in therapy of PCSK9 inhibitors. The 2013 consensus guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC) emphasize the use of statin therapy with intensity stratified by risk level.[2] This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[3] Significant discussion exists in the provider community over the best approach to treatment.

  Recently in November 2014, results of the IMPROVE-IT trial supported the use of LDL-C target goals. In this trial, patients who had been hospitalized for an acute coronary syndrome within the preceding ten days were randomized to simvastatin alone or in combination with ezetimibe (N=18,144). The combination treatment group achieved an average lower LDL-C (53.7 mg/dL vs 69.5 mg/dL; P<0.001) and had a significantly lower event rate at seven years (32.7% vs 34.7%; P=0.016). The investigators concluded that “lowering LDL-C to levels below previous targets provided additional benefit” reemphasizing the use of LDL-C target goals as a marker of cholesterol response.[4]

  As noted above, the ACC/AHA guidelines do not address the place in therapy of the PCSK9 inhibitors. However, the ACC president addressed the issue in a press release upon the approval of Praluent® (alirocumab):

  > "The ACC eagerly awaits the results of the clinical trials that are in progress. In the meantime, we continue to recommend physicians limit prescribing to the very high risk, hard-to-treat groups approved by the FDA and otherwise follow the current guidelines, which recommend lifestyle change and, if needed, statins for most patients with or at risk of heart disease. Improving diet and optimizing exercise are the cornerstones of heart disease management and prevention. Statins are available as low-cost generics, are well tolerated in most patients, and their effectiveness is supported by strong evidence."[5]

Table 1. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Alirocumab	HeFH or clinical atherosclerotic cardiovascular disease: Injection: initial, 75 mg SQ every two weeks; maintenance and maximum, 150 mg SQ every two weeks	Safety and efficacy in children have not been established.	Prefilled Pen: 75 mg 150 mg Prefilled Syringe: 75 mg 150 mg

Evidence-based Medicine

- The FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (>5,000 patients). These trials include patients with HeFH, those with coronary heart disease (CHD) and those at risk for cardiovascular events (CVE).[1, 6-17]
- Across the clinical trial program, the agent was associated with an approximate 40% to 60% decrease in LDL-C from baseline.
    - In addition, other lipid measures generally decreased at higher levels than with placebo.
    - In several studies, the majority of patients were able to reach goal LDL-C levels by week 12 without requiring dose titration. For example, in ODYSSEY COMBO I, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose throughout the study.[1,6-17]
- In a post-hoc analysis of one key study, ODYSSEY LONG-TERM, investigators observed a decreased risk of cardiovascular events compared to placebo (1.7% vs 3.3%; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.31 to 0.90; P=0.02).[14]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The use of PCSK9 inhibitors are not addressed.
    - AHA/ACC guidelines emphasize the use of statin therapy with intensity stratified by risk level.[2]
    - This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[3]

- Other Key Facts:
    - This agent has been studied in a wide population including patients with HeFH, in combination with a statin, in statin intolerant patients and in patients with a high risk of cardiovascular events or prior history of these events.1,6-17
    - This agent is generally well tolerated, with few clinically significant adverse drug reaction.

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New Drug Review
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Although the agent has demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, the agent was only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1]

Currently available consensus treatment guidelines do not address the place in therapy of PCSK9 inhibitors. The 2013 consensus guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC) emphasize the use of statin therapy with intensity stratified by risk level.[2] This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[3] Significant discussion exists in the provider community over the best approach to treatment. These guidelines are summarized below in Table 7.

Recently in November 2014, results of the IMPROVE-IT trial supported the use of LDL-C target goals. In this trial, patients who had been hospitalized for an acute coronary syndrome within the preceding ten days were randomized to simvastatin alone or in combination with ezetimibe (N=18,144). The combination treatment group achieved an average lower LDL-C (53.7 mg/dL vs 69.5 mg/dL; P<0.001) and had a significantly lower event rate at seven years (32.7% vs 34.7%; P=0.016). The investigators concluded that “lowering LDL-C to levels below previous targets provided additional benefit” reemphasizing the use of LDL-C target goals as a marker of cholesterol response.[4]

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Indications

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

Pharmacokinetics

Table 1. Pharmacokinetics[1]

Generic Name	Bioavailability (%)	Volume of Distribution (L/kg)	Elimination	Serum Half-Life (days)
Alirocumab	85%	0.04 to 0.05	Protein degradation	17 to 20

Clinical Trials

The FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (>5,000 patients). These trials include patients with HeFH, those with coronary heart disease (CHD) and those at risk for cardiovascular events (CVE).[1, 6-17]

Across the clinical trial program, the agent was associated with an approximate 40% to 60% decrease in LDL-C from baseline. In addition, other lipid measures generally decreased at higher levels than with placebo. Most studies evaluated a protocol in which patients started at 75 mg every two weeks and were increased to 150 mg if LDL was above 70 mg/dL at week 12. In several studies, the majority of patients were able to reach goal LDL-C levels by week 12 without requiring dose titration. For example, in ODYSSEY COMBO I, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose throughout the study. ODYSSEY CHOICE I also evaluated alirocumab at a dose of 300 mg every four weeks; however, the agent did not receive approval for use at this dose.[1,6-17]

In a post-hoc analysis of one key study, ODYSSEY LONG-TERM, investigators observed a decreased risk of cardiovascular events compared to placebo (1.7% vs 3.3%; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.31 to 0.90; P=0.02).[14]

Five of these studies have been published (ODYSSEY COMBO I and II, ODYSSEY LONG TERM, ODYSSEY MONO and ODYSSEY OPTIONS I). The remaining seven studies have results available through manufacturer press releases and/or conference abstracts. [1,6-17] Published studies are summarized below in Table 2.

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kereiakes et al[9,10] ODYSSEY COMBO I Alirocumab 75 mg SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs placebo Patients continued to take statin therapy with or without other lipid lowering therapy.	DB, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥100 mg/dL and no established heart disease but at a high risk for CVE† and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening	N=316 52 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Percentage of patients achieving LDL-C <70 mg/dL, other lipid parameters and safety evaluations	Primary: Alirocumab was associated with a significantly greater reduction in LDL-C from baseline to week 24 compared with placebo (48.2% vs 2.3%; P<0.0001). At week 12, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose. In patients with a dose increase, LDL-C was reduced by an additional mean 22.8% at week 24 compared with week 12. These patients achieved similar reductions in LDL-C as those not requiring a dose increase (N=32). Secondary: LDL-C <70 mg/dL was achieved by 75% of the alirocumab group compared to 9% of the placebo group at week 24. Significant reductions from baseline to week 24 after therapy with alirocumab (P<0.0001 vs placebo) were observed in non–HDL-C (−39.1% vs −1.6%), apoB (−36.7% vs −0.9%), TC (−27.9% vs −2.9%), and lipoprotein(a) (−20.5% vs −5.9%). No significant change was observed in TG levels; whereas, a significant increase in HDL-C was observed in the alirocumab group (3.5% vs −3.8%; P<0.0001). The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups.
Cannon et al[10,11] ODYSSEY COMBO II Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥1.8 mmol/L) vs ezetimibe 10 mg QD	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and no established heart disease but at a high	N=720 104 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations	Primary: Alirocumab was associated with a significantly greater reduction in mean LDL-C from baseline at week 24 compared to ezetimibe (50.6 ± 1.4% vs 20.7 ± 1.9%; 29.8% ± 2.3% difference; P<0.0001). Secondary: Seventy seven percent of alirocumab and 45.6% of ezetimibe patients achieved LDL-C <1.8 mmol/L (P<0.0001). As compared with the ezetimibe group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and had a modest increase in levels of HDL-C (P<0.0001

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients continued to take statin therapy. Other lipid lowering therapy was not permitted. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	risk for CVE† and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening		and safety evaluations	for all comparisons). TG were reduced from baseline to week 24 by 13.0 ± 1.5% in the alirocumab group and by 12.8 ± 2.0% in the ezetimibe group, but the difference between treatment arms was not statistically significant. Alirocumab was generally well tolerated, with no evidence of an excess of treatment-emergent adverse events. Adjudicated cardiovascular events were infrequent, occurring in 4.8% (n=23) of the alirocumab group vs 3.7% (n=9) in the ezetimibe group. Treatment-emergent local injection site reactions occurred in 2.5% of patients in the alirocumab arm vs 0.8% for ezetimibe arm.
Robinson et al[14] ODYSSEY LONG TERM Alirocumab 150 mg injected SQ every two weeks vs placebo Patients continued to take statin therapy with or without other lipid lowering agents. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet	DB, MC, PC, RCT Patients ≥18 years of age at a high risk for CVE† (with HeFH or with established heart disease or CHD equivalent) with LDL ≥70 mg/dL receiving statins at maximum tolerated dosage for at least four weeks before screening	N=2,341 78 weeks	Primary: Percent change from baseline in LDL-C at week 24 Secondary: Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations, major cardiovascular events (death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization), adherence rates and safety evaluations	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to placebo (−61.0% vs 0.08%;−62% placebo-corrected difference; P<0.0001). This effect remained consistent over 78 weeks. Secondary: The mean absolute LDL-C level at week 24 was 48 mg/dL in the alirocumab group and 119 mg/dL in the placebo group, corresponding to a mean absolute change from baseline of −74 mg/dL and −4 mg/dL, respectively (P<0.0001). The goal of an LDL-C level of <70 mg/dL at week 24 was met by 79.3% of the patients in the alirocumab group compared to 8.0% of the patients in the placebo group (P<0.001). As compared with the placebo group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and triglycerides and had a modest increase in levels of HDL-C and apolipoprotein A1 (P<0.001 for all comparisons). In a post hoc analysis, the rate of major adverse cardiovascular events

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for the duration of the study.				was lower with alirocumab than with placebo (1.7% vs 3.3%; HR, 0.52; 95% CI, 0.31 to 0.90; P=0.02). Adherence was 98.0% and 97.6% in the alirocumab group and the placebo group, respectively. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%).
Roth et al[15] ODYSSEY MONO Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 8 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD	DB, MC, PC, RCT Patients with primary hyper-cholesterolemia and moderate risk for CVE[†] and LDL-C ≥100mg/ dL and ≤190mg/dL	N=103 34 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to ezetimibe (47.2% vs 15.6%; P<0.0001). Secondary: Safety parameters and adverse events were similar between the two groups. The most common class of adverse events was infections (39.2% with ezetimibe vs 42.3% with alirocumab), which included nasopharyngitis, influenza, and upper respiratory tract infection. Injection-site reactions occurred in less than 2% of patients in both groups. Muscle-related adverse events occurred in 3.9% of patients treated with ezetimibe and 3.8% of patients treated with alirocumab.
Bays et al[16,17] ODYSSEY OPTIONS I Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD vs	AC, DB, MC, PG, RCT Patients ≥18 years of age with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and risk factors for CVE[†]	N=355 24 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: Among atorvastatin 20 and 40 mg regimens respectively, there was a significantly greater decrease in LDL-C with alirocumab add-on from baseline at week 24 compared to add-on ezetimibe, double dose atorvastatin and switching to rosuvastatin (44.1% and 54.0% vs 20.5% and 22.6%, 5.0% and 4.8%, and 21.4%; P<0.001 vs all comparators). Most alirocumab-treated patients (86%) maintained their 75 mg every two weeks regimen. Secondary: Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, compare to 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data pooled).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin (at double baseline dose) vs rosuvastatin 40 mg QD (atorvastatin 40 mg baseline dose cohort only) Prior to randomization, patients were stabilized on atorvastatin 20 mg to 40 mg QD.				

†In this trial, high risk for cardiovascular events was defined as: ischemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥2 additional risk factors (hypertension; ankle–brachial index of ≤0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or a family history of premature coronary heart disease).
Drug regimen abbreviations: QD=once daily, SQ=subcutaneously
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
apoB=apolipoprotein B, ATP=Adult Treatment Program, CHD=coronary heart disease, CI=confidence interval, CVE=cardiovascular events, HDL-C=high density lipoprotein, HeFH=heterozygous familial hypercholesterolemia, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, TC=total cholesterol, TG=triglyceride

Special Populations

Table 3. Special Populations[1]

Population	Precaution
Elderly	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.
Renal Dysfunction	No dose adjustment is needed for patients with mild or moderately impaired renal function. No data are available in patients with severe renal impairment.*
Hepatic Dysfunction	No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment.*
Pregnancy / Nursing	There are no available data on use of alirocumab in pregnant women to inform a drug-associated risk. The FDA's experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester. Consider the benefits and risks of treatment and possible risks to the fetus before prescribing to pregnant women. There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for treatment and any potential adverse effects on the breastfed infant from the agent or from the underlying maternal condition.
Children	Safety and efficacy in children have not been established.
Age Restrictions	FDA approved for use in patients ages ≥18 years.

*No adequate or well-controlled trials.

Adverse Drug Events

The safety of alirocumab was evaluated in nine placebo-controlled trials (N=2476). At baseline, 37% of patients had a diagnosis of HeFH and 66% had clinical atherosclerotic cardiovascular disease. Adverse reactions reported in ≥2% of alirocumab-treated patients, and more frequently than in placebo-treated patients, are shown in Table 5. Rare side effects included: neurocognitive events, liver enzyme abnormalities and allergic reactions.

Neurocognitive events were reported in 0.8% of patients treated with alirocumab and 0.7% of patients treated with placebo. Confusion or memory impairment were reported more frequently (0.2% for each) than in those treated with placebo (<0.1% for each).

Liver-related disorders (primarily related to abnormalities in liver enzymes) were reported in 2.5% of patients treated with alirocumab and 1.8% of patients treated with placebo, leading to treatment discontinuation in 0.4% and 0.2% of patients, respectively. Increases in serum transaminases to greater than three times the upper limit of normal occurred in 1.7% of patients compared to 1.4% treated with placebo.
Allergic reactions were reported more frequently in patients treated with alirocumab than in those treated with placebo (8.6% vs. 7.8%). The proportion of patients who discontinued treatment due to allergic

reactions was higher among those treated with alirocumab (0.6% vs. 0.2%). Serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported in patients using alirocumab in controlled clinical trials.

Table 4. Adverse Events Occurring in Greater Than or Equal to 2% of Alirocumab-Treated Patients and More Frequently Than with Placebo[1]

Adverse Event	Reported Frequency	
	Alirocumab 75 mg to 150 mg every two weeks %, N=2476	Placebo %, N=1276
Nasopharyngitis	11.3	11.1
Injection site reactions	7.2	5.1
Influenza	5.7	4.6
Urinary tract infection	4.8	4.6
Diarrhea	4.7	4.4
Bronchitis	4.3	3.8
Myalgia	4.2	3.4
Muscle spasms	3.1	2.4
Sinusitis	3.0	2.7
Cough	2.5	2.3
Contusion	2.1	1.3
Musculoskeletal pain	2.1	1.6

Contraindications and Warnings/Precautions

Table 5. Contraindications and Warning/Precautions[1]

Contraindication	Hypersensitivity; alirocumab should not be used in patients with known hypersensitivity. Reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization.
Warning/ Precaution	Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with treatment. If signs or symptoms of serious allergic reactions occur, discontinue alirocumab, treat and monitor until signs and symptoms resolve.

Drug Interactions

There are no known clinically significant drug interactions with alirocumab. However, the median apparent half-life of alirocumab is reduced to 12 days when administered with a statin. This difference is not clinically meaningful and does not impact dosing recommendations.[1]

Dosage and Administration

Prior to administration, alirocumab should be refrigerated and then warmed for 30 to 40 minutes to room temperature. The agent should administered every two weeks subcutaneously in rotating injection sites starting at a dose of 75 mg. LDL-C should be monitored within four to eight weeks, and dose increase to 150 mg may be considered if not at LDL-C goal.[1]

Table 6. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
alirocumab	HeFH or clinical atherosclerotic cardiovascular disease: Injection: initial, 75 mg SQ every two weeks; maintenance and maximum,	Safety and efficacy in children have not been established.	Prefilled Pen: 75 mg 150 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	150 mg SQ every two weeks		Prefilled Syringe: 75 mg 150 mg

Drug regimen abbreviations: SQ=subcutaneously
HeFH=heterozygous familial hypercholesterolemia

Clinical Guidelines

Table 7. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[2]	Statin treatment · The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD. · High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. · In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. · In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. · Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (ten-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. · For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. · For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions and consider patient preferences. · Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. · High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated ten-year ASCVD risk unless contraindicated. · In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. · Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk ≥7.5% should

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	be treated with moderate- to high-intensity statin therapy. · It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk of 5.0 to <7.5%. · Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions and patient preferences for treatment. · In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> · To maximize the safety of statins, selection of the appropriate statin and dose in men and non-pregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. · Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. · Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. · Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. · Creatinine kinase should not be routinely measured in individuals receiving statin therapy. · Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. · During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. · Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy.

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	· During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). · Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. · It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. · Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. · For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV) . A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). · It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. · If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original

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	dose. · For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. Monitoring and optimizing statin therapy · Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. · The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. · Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. · It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. · Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. · Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. · In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Non statin safety · Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter.

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	· Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. · In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. · To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. · Bile acid sequestrants should not be used in individuals with baseline fasting TG levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe TG elevations might occur. · A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. · It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. · It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. · Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. · Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. · Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. · Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. · If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day.

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	· If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. · If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[3]	· TLC remain an essential modality in clinical management. · When LDL-C lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. · Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). · When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. · Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins. · In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. · Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> · Begin LDL-C lowering drugs in young adulthood. · TLC indicated for all persons. · Statins, first line of therapy (start dietary therapy simultaneously). · Bile acid sequestrants (if necessary in combination with statins). · If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> · Statins may be moderately effective in some persons. · LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> · TLC indicated. · All LDL-C lowering drugs are effective. · Combined drug therapy required less often than in heterozygous familial

Clinical Guideline	Recommendations
	hypercholesterolemia. Treatment of polygenic hypercholesterolemia · TLC indicated for all persons. · All LDL-C lowering drugs are effective. · If necessary to reach LDL-C goals, consider combined drug therapy.

ASCVD=atherosclerotic cardiovascular disease, CHD=coronary heart disease, HDL-C=high density lipoprotein, HIV=human immunodeficiency virus, LDL-C=low density lipoprotein cholesterol, TG=triglycerides, TLC=therapeutic lifestyle changes

Conclusions

Praluent® (alirocumab) is FDA-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C. Although the agent has demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, the agent was only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1]

The FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (>5,000 patients). These trials include patients with HeFH, those with CHD and those at risk for CVE. Across the clinical trial program, the agent was generally associated with an approximate 40% to 60% decrease in LDL-C from baseline. In general, the majority of patients in trials achieved this goal without requiring dose titration to the 150 mg dose. In addition, other lipid measures generally decreased at higher levels than with placebo. Across these clinical trials, the agent was well tolerated. [1,6-17]

In a post-hoc analysis of one key study, ODYSSEY LONG-TERM, investigators observed a decreased risk of cardiovascular events compared to placebo (1.7% vs 3.3%; HR 0.52; 95% CI, 0.31 to 0.90; P=0.02).[14] This data is considered preliminary as the prescribing information states that the agent has not demonstrated a benefit on cardiovascular morbidity and mortality.[1] Additional cardiovascular data is expected upon completion of the ODYSSEY OUTCOMES trial.

Currently available consensus treatment guidelines do not address the place in therapy of PCSK9 inhibitors. The 2013 consensus guidelines from the AHA/ACC emphasize the use of statin therapy with intensity stratified by risk level.[2] This differed significantly from the previous gold standard guidelines from the National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[3] Significant discussion exists in the provider community over the best approach to treatment.

Due to the lack of consensus among experts in the cardiology field, it is difficult to predict the place in therapy of the agent. In addition, the agent was studied in several populations for which FDA-approval was not granted including patients at high risk for CVE (without clinical ASCVD) and patients demonstrated to be statin-intolerant who cannot use the agent as adjunctive therapy. [1,6-17] The agent also is significantly more costly than statin therapy and ezetimibe. Therefore, the agent will most likely be an appropriate therapy for patients with a history of a cardiovascular event or documented HeFH, who cannot reach LDL-C goals (<70 mg/dL) on maximum statin therapy and/or ezetimibe and who are under the care of a cardiologist.

References

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DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Praluent (alirocumab) is subject to prior authorization.

1. Coverage and limitations:

Authorization will be given if the following criteria are met and documented:

Initial Requests

A. One of the following:
   i. Recipient has a diagnosis of heterozygous familial hypercholesterolemia (HeFH)
   OR
   ii. Patient has clinical atherosclerotic cardiovascular disease and requires additional lowering of LDL-C (defined as acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin).

   AND

B. Prescribed by or in consultation with a cardiologist or lipid specialist
   AND
C. Will be used as an adjunct to a low-fat diet and exercise
   AND
D. One of the following:

   i. The recipient has had an inadequate response to high intensity statin therapy defined as ALL of the following:
      a. Has received therapy with atorvastatin ≥40 mg or rosuvastatin ≥20 mg for at least the past three months
      b. Has received add-on therapy with ezetimibe to the maximum tolerable dose of statin for at least the past three months or the recipient has a contraindication to ezetimibe therapy.
      c. LDL-C after therapy for at least the past three months was ≥100 mg/dL (HeFH) or ≥70 mg/dL (clinical atherosclerotic cardiovascular disease)
      d. Statin therapy will be continued with PCSK9 therapy

   OR

   ii. The recipient has had an inadequate response to moderate intensity statin therapy defined as all of the following:
      a. Has an intolerance or contraindication to high-intensity statin therapy
      b. Has received therapy with atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin >20 mg, pravastatin >40 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg twice daily, or pitavastatin >2 mg for at least the past three months
      c. Has received add-on therapy with ezetimibe to the maximum tolerable dose of statin for at least the past three months or the recipient has a contraindication to ezetimibe therapy
      d. LDL-C after therapy for at least the past three months was ≥100 mg/dL (HeFH) or ≥70 mg/dL (clinical atherosclerotic cardiovascular disease)
      e. Statin therapy will be continued with PCSK9 therapy

   OR

iii. The recipient experienced an adverse reaction to at least two statins; the statins and adverse reactions must be documented in the recipient's medical record

OR

iv. The recipient has a labeled contraindication to all statins; the contraindication as documented in the recipient's medical record

Recertification Requests

A. The recipient has been adherent with PCSK-9 inhibitor therapy
AND
B. The recipient has been adherent with statin therapy OR the recipient has a labeled contraindication to statin therapy
AND
C. The recipient is continuing a low-fat diet and exercise regimen
AND
D. The recipient has achieved a reduction in LDL-C level.

2. Prior Authorization Guidelines:

A. Prior Authorization approval length will:
   i. Initial request: 6 months
   ii. Recertification requests: 1 year

3. Quantity Limitations:

A. 2 pens or syringes/28 days