VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors – Praluent® (alirocumab injection for subcutaneous use – sanofi-aventis/Regeneron)

TAC APPROVAL DATE: 06/12/2019

OVERVIEW

Praluent, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated 1) to reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease; and 2) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C).[1] The safety and efficacy of Praluent in children have not been established.

Clinical Data

The efficacy of Praluent was assessed in several studies which mainly involved patients at high risk (e.g., background atherosclerotic cardiovascular disease, HeFH) who received Praluent along with maximally tolerated doses of statins, with or without other lipid-modifying therapies. The LDL-C reductions when Praluent was added onto statin therapy ranged from approximately 50% to 60% at the time of the efficacy endpoint evaluations (e.g., 12 or 24 weeks). Longer-term follow-up, including extension studies, are also available.[1]

ODYSSEY Outcomes was a Phase III, multicenter, international, randomized, double-blind, placebo-controlled cardiovascular (CV) outcomes trial involving Praluent (75 or 150 mg SC once every 2 weeks [Q2W]) used in addition to maximally tolerated statin therapy (n = 18,924) for up to 5 years among patients who had experienced a recent acute coronary syndrome (ACS) event.[1,2] The trial included patients who were ≥ 40 years of age who had experienced an ACS event (acute MI [83%] or unstable angina [17%]) within 1 to 12 months prior to randomization. Those involved in the trial had inadequate control of lipids (e.g., LDL-C ≥ 70 mg/mL, non high-density lipoprotein cholesterol [non-HDL-C] ≥ 100 mg/dL) despite receipt of high-intensity statins (atorvastatin 40 mg or 80 mg daily or rosuvastatin 20 or 40 mg daily) or maximally tolerated statins, with or without other lipid-modifying therapy. The primary endpoint was the time to the first occurrence of one of the following: coronary heart disease (CHD) death, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina that required hospitalization. Other secondary endpoints were also evaluated (CV death, all-cause death, major CHD event). The mean patients age at baseline was 59 years and the mean LDL-C was 93 mg/dL.[1,2] Most patients (89%) were receiving high-dose atorvastatin (40 to 80 mg once daily [QD]) or rosuvastatin (20 to 40 mg QD); 8.5% of patients were on low to moderate dose atorvastatin/rosuvastatin and 3% of patients were on ezetimibe (with or without statin therapy).[2] The follow-up was a median of 2.8 years. At 4 months post-randomization, the mean LDL-C levels were 37.6 mg/dL and 93.3 mg/dL (on-treatment analysis), respectively, representing an approximate 62.7% decrease in LDL-C levels with adding Praluent. The primary endpoint occurred in 9.5% of patients (n = 903/9.462) given Praluent compared with 11.1% of patients (n = 1,052/9,462) given placebo (P < 0.001).[1,2] The number needed to treat to prevent one event was 63 patients. The event rates for the percentages of patients that comprised the primary endpoint (Praluent vs. placebo) included CHD death (2.2% vs. 2.3%; P = 0.38), non-fatal MI (6.6% vs. 7.6%), ischemic stroke (1.2% vs. 1.6%), and unstable angina (0.4% vs. 0.6%). All-cause death was also lower among patients assigned to Praluent (3.5%; n = 334/9,462) compared with placebo (4.1%; n = 392/9,462).

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.[3-9] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg QD and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. Other statin regimens, including atorvastatin and rosuvastatin at lower doses are classified as moderate-intensity (LDL-C reductions of 30% to 49%) products and low-intensity agents (LDL-C reductions < 30%). The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on the management of blood cholesterol (2018) defines ACSVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD).[3,4] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended in for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins. Additionally, guidelines and reviews have recognized that patients with a coronary artery calcium (CAC) score ≥ 300 Agatston units are at an increased risk of CV events.[10-13]

The National Lipid Association (NLA) published guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH.[14] FH encompasses a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. HeFH occurs in approximately 1 in 300 to 500 patients and is present in childhood. Total cholesterol (total-C) levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with FH. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with FH due to the markedly elevated LDL-C levels. In the pivotal trials for Praluent, HeFH was diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria.[1] In an AHA scientific statement, it describes the Dutch Lipid Clinical Network Criteria and states that a score of > 5 on the scale makes the diagnosis of FH highly probable.[15] Also, genetic testing can reveal a diagnosis of HeFH and clinical manifestations (e.g., tendon xanthomata) are highly suggestive of the condition.[15,16] Also, patients with an untreated LDL-C ≥ 190 mg/dL suggest FH. In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended. The addition of a PCSK9 inhibitor to statin therapy can be considered if this goal is not achieved.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.[17] In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which led to reductions in CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised CK levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients were believing that they were "statin intolerant". However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data supports this occurrence.[18-20]

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Praluent. Because of the specialized skills required for evaluation and monitoring of this new therapy, approval requires Praluent to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Praluent is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Atherosclerotic Cardiovascular Disease (ASCVD) [Clinical].*** Approve Praluent for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** The patient is aged ≥ 18 years; AND
   - **B)** The patient has had one of the following conditions or diagnoses (i, ii, iii, iv, or v):
     - **i.** The patient has had a previous myocardial infarction (MI) or has a history of an acute coronary syndrome (ACS); OR
     - **ii.** The patient has a diagnosis of angina (stable or unstable); OR
     - **iii.** The patient has a past history of stroke or transient ischemic attack (TIA); OR
     - **iv.** The patient has peripheral arterial disease (PAD); OR
     - **v.** The patient has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], angioplasty, coronary stent procedure); AND
   - **C)** The patient meets one of the following criteria (i or ii):
     - **i.** The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks AND the LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
     - **ii.** The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
       - **a)** The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR
       - **b)** The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
         - **(1)** The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
         - **(2)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g.,

myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

D) Praluent is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

2. Heterozygous Familial Hypercholesterolemia [HeFH].* Approve Praluent for 3 years if the patient meets the following criteria (A, B, C, and D):

A) The patient is aged ≥ 18 years; AND

B) The patient meets one of the following criteria (i, ii, iii, iv, or v):

i. The patient has an untreated LDL-C ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

ii. The patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene; OR

iii. The patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):

a) The prescriber used the Dutch Lipid Network criteria and the patient has a score > 5; OR

b) The prescriber used the Simon Broome criteria and the patient met the threshold for "definite" or "possible" familial hypercholesterolemia; OR

iv. The patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); OR

v. The patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 100 mg/dL (after treatment with antihyperlipidemic agents but prior to PCSK9 inhibitor therapy such as Praluent [alirocumab injection for SC use] or Repatha [evolocumab injection for SC use]); AND

C) The patient meets one of the following criteria (i or ii):

i. The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product])* for ≥ 8 continuous weeks AND the LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR

b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:

(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

D) Praluent is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

3. Primary Hyperlipidemia (not associated with ASCVD, HeFH, or HoFH).* [Note: This may be referred to as combined hyperlipidemia, hypercholesterolemia {pure, primary}, dyslipidemia, increased/elevated LDL-C]. Approve Praluent for 3 years if the patient meets the following criteria (A, B, C, and D):

A) The patient is aged ≥ 18 years; AND

B) The patient has a coronary artery calcium or calcification (CAC) score ≥ 300 Agatston units; AND

C) The patient meets one of the following criteria (i or ii):

i. The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]) AND ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND the LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR

ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR

b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:

(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

D) Praluent is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

Note:
* Patients may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable. (e.g., patients with HeFH have had a clinical ASCVD event, patients with primary hyperlipidemia may have HeFH).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Praluent has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent use of Praluent with Repatha® (evolocumab injection for SC use) or Juxtapid® (lomitapide capsules).** Repatha is another PCSK9 inhibitor and should not be used with Praluent.[21] Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with homozygous familial hypercholesterolemia (HoFH).[22] The efficacy and safety of Repatha or Juxtapid in combination with Praluent have not been established.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Selected revision	Added additional diagnostic criteria defining HeFH as follows: LDL-C ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); the patient has genetic confirmation of HeFH; the patient has been diagnosed with HeFH meeting one of the following criteria thresholds of Dutch Lipid Network criteria score > 5 or Simon Broome criteria with "definite" or "possible" FH; or the patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma).	01/25/2017
Selected revision	Treatment duration for all indications changed from 12 months to 3 years.	04/12/2017
Annual revision	For the criteria regarding clinical ASCVD, clarified that patients that only report having carotid artery stenosis and/or an elevated calcium score do not meet the requirements for clinical ASCVD.	09/13/2017
Early annual revision	For the diagnosis regarding clinical ASCVD, the criteria that the patient have an LDL-C level ≥ 70 mg/dL (after treatment with antihyperlipidemia agents but prior to PCSK9 inhibitor therapy) was removed.	02/21/2018
Early annual revision	For the indications regarding HeFH and ASCVD, added in documentation requirement for initial review. Also, the requirement that be tried (in combination with the high-intensity statin) for 8 weeks was removed; the requirement for a previous 8-week trial of a high-intensity statin (or intolerance) remains in the policy [effective 7/1/2018].	05/02/2018
Early annual revision	For the criteria that addresses the diagnosis of HeFH among patients who have received treatment with antihyperlipidemic agents but prior to PCSK9 inhibitor therapy (such as Praluent and Repatha), changed the LDL-C level from ≥ 160 mg/dL to ≥ 100 mg/dL [effective 7/1/2018].	05/09/2018
Early annual revision	Documentation removed from the Policy that was set to be effective on 7/1/2018.	05/16/2018
Annual revision	1. **Primary Hyperlipidemia** (not associated with Atherosclerotic Cardiovascular Disease, Heterozygous Familial Hypercholesterolemia, or Homozygous Familial Hypercholesterolemia): This new Food and Drug Administration (FDA)-approved indication was added as an approval for a 3-years duration in patients ≥ 18 years of age who meet several other required criteria. See policy for details. 2. **Conditions Not Recommended for Approval**: Kynamro was removed from the list of agents in which Praluent should not be used with concomitantly because this product is no longer available.	06/12/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; P & T – Express Scripts Pharmacy and Therapeutics Committee; TAC – Therapeutic Assessment Committee; HeFH – Heterozygous familial hypercholesterolemia; ASCVD – Atherosclerotic cardiovascular disease; PCSK9 – Proprotein convertase subtilisin kexin type 9; DEU – Drug Evaluation Unit; PA – Prior authorization; LDL-C – Low-density lipoprotein cholesterol; FH – Familial hypercholesterolemia; ASCVD – Atherosclerotic cardiovascular disease.

APPENDIX A.
Simon Broome Register Diagnostic Criteria[15]

Definite Familial Hypercholesterolemia:

a) Raised cholesterol
   (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);

b) AND
   (i) Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);

c) OR
   (i) DNA-based evidence of LDL-receptor, familial defective apo B-100, or PCSK9 mutation.

Possible Familial Hypercholesterolemia:

a) Raised cholesterol
   (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult;

b) AND at least one of the following:
   (i) Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;

c) OR
   (i) Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

APPENDIX B.
Dutch Lipid Network Criteria for Familial Hypercholesterolemia[16]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.