Pharmacy Management Drug Policy

SUBJECT: PCSK9 Inhibitors; Praluent™ (alirocumab), Repatha™(evolocumab)
POLICY NUMBER: Pharmacy-61
EFFECTIVE DATE: 8/15
LAST REVIEW DATE: 9/20/2019

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. Medical or drug policies apply to commercial and Health Care Reform products only when a contract benefit for the specific service exists.

DESCRIPTION:

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a novel class of medications to treat hypercholesteremia. PSCK9 is a regulatory serine protease that increases circulating levels of low-density lipid cholesterol (LDL-C). PSCK9 binding leads to a degradation of LDL receptors and a corresponding inhibition of LDL-C breakdown. By inhibiting the binding of PCSK9 to LDL receptors, the PCSK9 inhibitors have been shown in clinical trials to induce potent lowering of LDL-C.

Praluent is indicated:

- to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.
- as 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) to reduce low-density lipoprotein cholesterol LDL-C.

Repatha is indicated:

- to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease;
- as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).
- as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

On 12/1/2017, Amgen, the manufacturer of Repatha, issued an announcement that the FDA has approved the drug for primary hyperlipidemia. As this term is not well defined in the dyslipidemia treatment guidelines, the plan sought clarification from the manufacturer and the FDA to accurately identify the patient population targeted by the new indication. It was clarified that primary hyperlipidemia is *not* primary prevention of ASCVD but refers broadly to the category of patients who have some genetic component to their hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH). This broadened the indication from HeFH alone, but this broader patient population remains not well characterized by Amgen or the FDA. As such, without sufficient guidance to better define primary hyperlipemia, and as HeFH is the main component of this category, policy criteria will continue to focus on HeFH in terms of evaluating medically necessary use for this indication. Additionally, outcomes from the FOURIER trial led to the removal of the limitations of use previously listed on the package insert for Repatha. There was sufficient evidence from the study that the official indication could be updated to include risk reduction for myocardial infarction, stroke,

and coronary revascularization in adults with established cardiovascular disease. The ODYSSEY OUTCOMES trial results similarly allowed the risk reduction indication update for Praluent in 4/2019.

There are many clinical guidelines available regarding the treatment of patients with dyslipidemia. Two nationally recognized organizations (the American College of Cardiology [ACC]/American Heart Association [AHA] and the National Lipid Association [NLA]) have guidelines regarding the management of patients with elevated cholesterol and related conditions.[2,3] In 2011, the NLA also published guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH.[4] Generally, statins are considered the mainstay of therapy. They can lower LDL-C by 30-50% and have been shown to reduce the risk of ASCVD and its associated mortality.[5] Furthermore, the addition of ezetimibe to statins has been shown to decrease LDL-C further and improve outcomes.[6]

The 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults promote a major change in hypercholesterolemia management.[2] Instead of focusing on LDL-C goals, they emphasize the benefits of LDL-C reduction and the appropriate intensity of statin therapy in those patients most likely to benefit. In contrast, the 2014 NLA recommendations for patient-centered management of dyslipidemia recommend treatment goals.[3] According to the guidelines, first-line treatment for dyslipidemia includes a moderate- or high-intensity statin. Patients at low, moderate, or high risk are recommended to obtain an LDL-C level <100mg/dL. Patients at very high risk (which includes patients with ASCVD) are recommended to achieve an LDL-C level <70 mg/dL. The 2011 NLA guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH, identify statins as the initial treatment for all adults with FH.[4] Higher risk patients may require intensification of drug therapy to achieve more aggressive treatment goals (LDL-C <100mg/dL). For all other patients, intensification of drug therapy may be considered if LDL-C remains ≥ 160mg/dL, or if an initial 50% reduction in LDL cholesterol is not achieved. Both the ACC/AHA and NLA guidelines for the management of lipid disorders also emphasize the importance of lifestyle modifications (which include a heart-healthy diet, regular exercise, avoidance of tobacco products, and maintenance of a healthy weight) as a component of ASCVD risk reduction. Lifestyle modifications should be initiated prior to and in concert with the use of cholesterol-lowering therapies.[2]

POLICY:

Based upon our assessment and review of the peer-reviewed literature, **Praluent™ and Repatha™** have been medically proven to be effective and therefore, **medically necessary** for the following:

1. **Therapy is prescribed by or in consultation with a cardiologist, endocrinologist, or lipidologist**

AND

2. **The patient is 18 years of age or older**
    a. **For patients with a diagnosis of HoFH, coverage will be allowed if the patient is ≥ 13 years of age**

AND

3. **The patient has one of the following diagnoses:**
    a. **Clinical atherosclerotic cardiovascular disease (ASCVD)**
        i. Must have a history of acute coronary syndrome, myocardial infarction (MI), stable or unstable angina, coronary/other arterial revascularization, stroke, TIA, peripheral arterial disease or other documented atherosclerotic disease (such as coronary atherosclerosis, renal atherosclerosis, aortic aneurysm secondary to atherosclerosis, or Carotid plaque with ≥ 50% stenosis) **OR**

    b. **Heterozygous Familial Hypercholesterolemia (HeFH)**

i. Molecular genetic testing must demonstrate evidence of an LDL-R mutation, familial defective apo B_{100}, or a PCSK9 mutation **OR**

ii. Diagnosis must be confirmed as "definite" according the World Health Organization Criteria (Dutch Lipid Network) OR Simon-Broome Register Diagnostic Criteria [Refer to **table 1** and **table 2** below]. Documentation of the following must be provided to calculate an accurate score:

1. Patient's first-degree relatives with ANY of the following:
    a. Tendon xanthoma
    b. Corneal arcus
    c. Known LDL-C >95th percentile by age and gender for country
    d. Known premature (<55 years, men <60 years, women) coronary heart disease (CHD)
2. Patient's child(ren) <18 years with LDL-C >95th percentile by age and gender for country
3. Patient's baseline LDL-C level prior to use of ALL-cholesterol lowering medications
4. Patient's history of CHD
5. Patient's history of cerebral or peripheral vascular disease
6. Physical exam finding of tendon xanthoma
7. Physical exam finding of corneal arcus **OR**

c. Primary Hyperlipidemia (REPATHA ONLY)

i. Primary hyperlipidemia should be considered a broader category than, but also containing, Heterozygous Familial Hypercholesterolemia (HeFH). It includes various phenotypes of genetically influenced hypercholesterolemia where LDL is over 190 mg/dL (Fredrickson classification). Specific genetic testing may not be available to suggest a genetic cause. Rather, a genetic association may be suspected in the context of optimized lifestyle modifications and risk factors.

ii. Requests will be evaluated for HeFH first. If a request does not meet the criteria for HEFH, then the provider will be required to submit adequate rationale in support of a diagnosis of primary hyperlipidemia. This must include current LDL over 190 mg/dL despite maximum tolerated statins and optimized lifestyle modifications and risk factors (see lifestyle modifications section below). Also, a distinction from primary prevention of ASCVD must be made. Use of Repatha for primary prevention of ASCVD is excluded. **OR**

d. Homozygous Familial Hypercholesterolemia (HoFH)

i. Molecular genetic testing must demonstrate evidence of an LDL-R mutation, familial defective apo B_{100}, or a PCSK9 mutation in both LDL-R alleles **OR**

ii. Must have history of an untreated LDL-C concentration >500mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents **OR**

iii. Must have untreated total cholesterol >500mg/dL AND triglycerides <300mg/dL AND both parents with documented untreated total cholesterol >250mg/dL

AND

4. **The patient has initiated all the following lifestyle modifications:** [documentation in progress notes must be received]
    - **a.** Must currently be a non-smoker.
        - **i.** Non-smoker is defined as someone who has not smoked in the past 6 months
    - **b.** Patient must be initiated on a heart-healthy diet
        - **i.** Diet must emphasize intake of vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, and non-tropical vegetable oils/nuts. Intake of sweets, sugar-sweetened beverages, and red meat should be limited.
    - **c.** Patient must engage in physical activity (at their level of ability) for at least 30 minutes most days of the week

AND

5. **Documentation of baseline LDL-C level must be provided-** measurement must occur within 60 days prior to treatment.

AND

6. **Has failed to reach target LDL-C while receiving treatment with highest available dose of high-intensity statin therapy (atorvastatin 80mg/day or rosuvastatin 40mg/day) for at least 8 weeks:**
    - **a.** For patients with HoFH who are undergoing apheresis, concurrent use of the highest available dose of high-intensity statin therapy is still required.
    - **b.** For patients with ASCVD, LDL –C must be ≥ 70mg/dL or
    - **c.** For patients with HeFH or HoFH, LDL-C must be ≥ 160mg/dL or
    - **d.** For patients with HeFH or HoFH and higher CHD risk, LDL-C must be ≥ 100mg/dL
        - **i.** Patients are at higher CHD risk if they have any of the following: diabetes, a family history of very early CHD (in men <45 years of age and women <55 years of age), high lipoprotein (a) ≥ 50mg/dL or 2 or more of the following CHD risk factors:

            1. ≥45 years of age if Male or ≥ 55 years of age if Female
            2. Family history of early CHD (<55 years of age in male first-degree relative or <65 years of age in female first-degree relative)
            3. High blood pressure (≥140/≥90 mmHg or on blood pressure medication)
            4. Low HDL-C (<40mg/dL if male or <50mg/dL if female)

    - **e.** Patient must be compliant with their previous statin therapy. Prescription drug claims from the last 6 months will be assessed for medication adherence. If pharmacy refill history is not available, a recent pharmacy profile will be requested. Progress notes documenting usage of sample medication may also be requested. A threshold of 80% PDC (Percent Days Covered) is typically defined as being compliant with drug therapy.
    - **f.** If patient is unable to tolerate statin therapy, documentation in progress notes must include:
        - **i.** A contraindication to statin therapy according to FDA labeling **OR**
        - **ii.** History of statin-related rhabdomyolysis
            1. Must have symptoms consistent with rhabdomyolysis (i.e.; muscle pain, swelling, and weakness, dark urine) AND
            2. Must have Creatine kinase (CK) level ≥ 10 times the upper limit of normal (ULN), Myoglobinuria, or acute renal failure (increase in serum creatinine >0.5 mg/dL) AND

3. Member was receiving a statin at the time of the event and symptoms resolved upon discontinuation of the statin **OR**

iii. History of statin intolerance. Documentation must include the following:

1. Inability to tolerate at least 2 different statins:
    a. At least 1 statin must be hydrophilic (such as pravastatin, fluvastatin, or Crestor) starting at the lowest starting average daily dose AND
2. Intolerance associated with confirmed, intolerable statin-related adverse effects(s) (i.e.; muscle related symptoms) or significant biomarker abnormalities (i.e.; ALT/AST >3 times the upper limit of normal accompanied by increases in total bilirubin >2 times the upper limit of normal) AND
3. Symptom or biomarker change, resolution, or significant improvement on dose decrease or discontinuation AND
4. Non-statin causes of muscle symptoms or biomarker abnormalities have been ruled out (For example, hypothyroidism, reduced renal function, reduced hepatic function, rheumatologic disorders such as polymyalgia rheumatic, steroid myopathy, vitamin D deficiency, or primary muscle disease)

AND

7. If patient can tolerate statins, Praluent or Repatha must be prescribed in combination with the maximum tolerated dose of a statin

AND

8. Approval Timeframes

1. Approvals for Repatha and Praluent <u>150mg</u> are for 12 months for both initial and recertification requests. Prescribing information recommends checking LDL 4-8 weeks after starting therapy (to ensure effectiveness). However, upon all recertifications (initial and subsequent), an LDL level measured within the past 12 months is required.

a. Initial Recertification require:

i. Demonstrated adequate reduction in LDL cholesterol defined as:

1. ≥40% reduction in LDL as compared to baseline LDL level or reduction to LDL goal for patients with a diagnosis of ASCVD or primary hyperlipidemia **OR**

2. Reduction in LDL level as compared to baseline LDL level for patients with a diagnosis of HeFH or HoFH **AND**

ii. Continued adherence to a high intensity statin at maximum tolerated dose **AND**

iii. Continued adherence to lifestyle modifications (non-smoker, diet, and exercise)

b. Subsequent Recertifications require:

i. Documentation that confirms the patient has maintained an adequate reduction in LDL cholesterol compared to baseline **AND**

ii. Continued adherence to a high intensity statin at maximum tolerated dose **AND**

iii. Continued adherence to lifestyle modifications (non-smoker, diet, and exercise)

2. **Initial approval for Praluent <u>75mg</u> is for 4 months. Recertification for Praluent <u>75mg</u> will be for 12 months.**
    a. **Initial Recertification require:**
        i. Demonstrated adequate reduction in LDL cholesterol defined as:
            1. ≥40% reduction in LDL as compared to baseline LDL level or reduction to LDL goal for patients with a diagnosis of ASCVD **OR**
            2. Reduction in LDL level as compared to baseline LDL level for patients with a diagnosis of HeFH or HoFH **AND**
        ii. Continued adherence to a high intensity statin at maximum tolerated dose **AND**
        iii. Continued adherence to lifestyle modifications (non-smoker, diet, and exercise)
    b. **Subsequent Recertifications require:**
        i. Documentation that confirms the patient has maintained an adequate reduction in LDL cholesterol compared to baseline (The LDL level must have been measured within the past 12 months) **AND**
        ii. Continued adherence to a high intensity statin at maximum tolerated dose **AND**
        iii. Continued adherence to lifestyle modifications (non-smoker, diet, and exercise)
    c. If adequate reduction in LDL is not achieved after 8 weeks on Praluent 75mg, then Praluent 150mg may be authorized for 3 months to evaluate effect on higher strength. Recertifications for Praluent 150mg thereafter will follow requirements for Praluent 150mg as outlined above.
3. **Approved Dosing**
    a. **Repatha**
        i. HoFH: 420 mg subcutaneously once monthly
        ii. HeFH/ASCVD/Primary hypercholesterolemia: 140 mg subcutaneously every 2 weeks OR 420 mg subcutaneously once monthly
    b. **Praluent**
        i. HoFH/HeFH/ASCVD: 75 mg subcutaneously every 2 weeks OR 150 mg subcutaneously every 2 weeks OR 300 mg subcutaneously once monthly
4. **Quantity Limit (QL)**
    a. **Repatha**
        i. Repatha Pushtronex® 420 mg/ 3.5 mL has a QL of 3.5 mL per 28 days
        ii. Repatha prefilled syringe 140 mg/mL has a QL of 2 mL per 28 days
        iii. Repatha prefilled SureClick® 140 mg/mL has a QL of 2 mL per 28 days
    b. **Praluent**
        i. Praluent pre-filled pen 75 mg/mL or 150 mg/mL has a QL of 2 mL per 28 days
        ii. Praluent pre-filled syringe 75 mg/mL or 150 mg/mL has a QL of 2 mL per 28 days

<u>POLICY GUIDELINES</u>:

1. Prior-authorization is contract dependent.

2. Praluent and Repatha will not be approved for use in combination with Juxtapid (lomitapide capsules) or Kynamro (mipomersen injection) as current medical literature does not currently support this.
3. Non-FDA approved indications for Praluent and Repatha will not be approved. Use of Repatha or Praluent for primary prevention of ASCVD is excluded.
4. For any diagnosis, if Praluent or Repatha therapy is initiated with samples and the member does not meet our criteria for coverage (as outlined above) before the start of Praluent/Repatha therapy, coverage of Praluent or Repatha will not be granted upon completion of samples.
5. The recommended starting dose for Praluent is 75mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150mg administered every 2 weeks.
6. Recommended dosing for Repatha is 140mg administered subcutaneously every 2 weeks or 420mg once monthly for primary hyperlipidemia with ASCVD or HeFH. For members with HoFH, the recommended dosing is 420mg once monthly.
7. LDL-C levels should be measured within 4 to 12 weeks of initiating or titrating Praluent or Repatha to assess response and adjust the dose, if needed.
8. Unless otherwise stated above within the individual drug criteria, approval time periods are listed in the table below.
    - Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary. Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e.; generics, biosimilars, or other guideline-supported treatment options). Requested dosing must continue to be consistent with FDA-approved or off-label/guideline-supported dosing recommendations.

Line of Business	Initial approval	Continued approval
Medicaid Managed Care (MMC) / Child Health Plus (CHP)	Praluent 75mg – 8 weeks Praluent 150mg – 12 months Repatha – 12 months	12 months
Commercial / Exchange	Praluent 75mg – 8 weeks Praluent 150mg – 12 months Repatha – 12 months	12 months

9. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are applicable, if trial of preferred drug(s) is the only criterion that is not met for a given condition, and one of the following circumstances can be substantiated by the requesting provider, then trial of the preferred drug(s) will not be required.

a. The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member;
b. The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen;
c. The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event;
d. The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities;
e. The individual is stable on the requested prescription drug. The medical profile of the individual (age, disease state, comorbidities), along with the rational for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.
f. The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug.

10. This policy is applicable to drugs that are included on a specific drug formulary. If a drug referenced in this policy is non-formulary, please reference the Coverage Exception Evaluation Policy for All Lines of Business Formularies policy for review guidelines.

CLINICAL CRITERIA FOR DIAGNOSIS OF HeFH

Table 1: Diagnostic Criteria for the Clinical Diagnosis of HeFH (WHO)

	Criteria	Score
Family history	First-degree relative known with premature CAD[a] and/or first-degree relative with LDL-C >95th percentile	1
	First-degree relative with tendon xanthomata and/or children <18 y with LDL-C >95th percentile	2
Clinical history	Patient has premature CAD[a]	2
	Patient has premature cerebral/peripheral vascular disease	1
Physical examination	Tendon xanthomata	6
	Arcus cornealis age <45 y	4
LDL-C	>8.5 mmol/L (> ≈330 mg/dL)	8
	6.5-8.4 mmol/L (≈250-329 mg/dL)	5
	5.0-6.4 mmol/L (≈190-249 mg/dL)	3
	4.0-4.9 mmol/L (≈155-189 mg/dL)	1
Definite FH		Score >8
Probable FH		Score 6-8
Possible FH		Score 3-5
No diagnosis		Score <3

CAD: coronary artery disease; FH: familial hypercholesterolemia; HeFH: heterozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; WHO: World Health Organization.
[a] Premature CAD: male before age 55, women before age 60.

Table 2: Simone-Broome Criteria for Diagnosis of FH

FH	Criteria
Definite	• TC >6.7 mmol/L or LDL-C >4.0 mmol/L in a child aged <16 y OR • TC >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult (levels either pretreatment or highest on-treatment) PLUS Tendon xanthomas in patient, or in first-degree relative (parent, sibling or child), or in second-degree relative (grandparent, uncle, or aunt) OR • DNA-based evidence of an LDL-R mutation, familial defective apo B_{100}, or a PCSK9 mutation.
Possible	• TC >6.7 mmol/L or LDL-C >4.0 mmol/L in a child aged <16 y OR • TC >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult (levels either pretreatment or highest on-treatment) AND AT LEAST ONE OF THE FOLLOWING • Family history of myocardial infarction: <50 y of age in second-degree relative or <60 y of age in first-degree relative • Family history of raised TC: >7.5 mmol/L in adult first- or second-degree relative or >6.7 mmol/L in child or sibling aged <16 y.

apo: apolipoprotein; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; LDL-R: low-density lipoprotein receptor; PCSK9: proprotein convertase subtilisin/kexin type 9; TC: total cholesterol.

UPDATES:

Date:	Revision:
10/19	Revision

9/19	Revision and P&T endorsement
6/19	Revision
1/19	Revision
9/18	Revision
8/17	Revision
8/16	Revision
3/16	Revision
11/15	Revision
10/15	Revision
9/15	Revision
8/15	Created

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