

## Pharmacy Policy Bulletin

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**Title:** Cholesterol Lowering Agents

**Policy #:** Rx.01.131

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***Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.***

***This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.***

***Members are advised to use participating pharmacies in order to receive the highest level of benefits.***

### ▸ Intent:

The intent of this policy is to communicate the medical necessity criteria for **lomitapide (Juxtapid®)**, **mipomersen (Kynamro®)**, **alirocumab (Praluent®)**, and **evolocumab (Repatha®)** as provided under the member's prescription drug benefit.

### ▸ Description:

**Lomitapide** a synthetic lipid-lowering agent, directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and very low-density lipoprotein (VLDL). The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

**Lomitapide** (Juxtapid®) is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

**Mipomersen** sodium is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis. Apo B is the principal apolipoprotein of LDL and its metabolic precursor, very low density lipoprotein (VLDL). Mipomersen Sodium inhibits synthesis of apo B by binding to its mRNA, resulting in degradation of the mRNA.

**Mipomersen sodium** (Kynamro®) is indicated as adjunct to lipid-lowering medications and diet to reduce low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Proprotein convertase subtilisin/ kexin type 9 (PCSK9) is a serine protease synthesized primarily by the liver and intestines. PCSK9 promotes the degradation of low density lipoprotein (LDL) receptors, thus preventing them from being recycled back to the plasma membrane where they can bind more LDL. Inhibitors of PCSK9 increase recycling of LDL receptors which in turn increases the capacity to remove LDL cholesterol (LDL-C) from the blood. These agents are monoclonal antibodies administered subcutaneously

**Alirocumab** (Praluent®) and **evolocumab** (Repatha®) are indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Evolocumab (Repatha) is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C.

According to current guidelines, HMG-CoA reductase inhibitors (statins) are the mainstay of pharmacologic therapy for treating elevated LDL-C for both primary and secondary prevention of atherosclerotic cardiovascular disease. Lifestyle modifications are a critical component of treating elevated LDL-C and should be used in conjunction with pharmacologic therapy.

Clinical trials of PCSK9 inhibitors demonstrated reductions in LDL-C approximately 50-60%. Reauthorization criteria will include a reduction from baseline of 25% or greater, which will assess adherence with the medication.

**Policy:**

Mipomerson sodium (Kynamro®) and Lomitapide (Juxtapid®) are approved when documentation is provided of ALL of the following:

1. Diagnosis of Homozygous Familial Hypercholesterolemia; and
2. Used as an adjunct to lipid lowering treatments and a low fat diet with ONE of the following:
  - a. Genetic confirmation of 2 mutant alleles at the LDL receptor. Apo B, PCSK9, or ARH adaptor protein gene locus
  - b. Untreated LDL-C > 500 mg/dL or treated LDL cholesterol ≥ 300 mg/dL or treated non-HDL cholesterol ≥ 330 mg/dL together with either of the following:
    - i. Cutaneous or tendonous xanthoma prior to 10 years of age
    - ii. Elevated LDL cholesterol prior to lipid-lowering therapy consistent with HeFH in both parents as listed below:

Age (years)	Total cholesterol (LDL cholesterol) (mg/dL)
< 18	220 (155)
20-29	240 (170)
30-39	270 (190)
≥ 40	290 (205)

3. ONE of the following:
  - a. Inadequate response to one of the following medications in combination with ezetimibe:
    - i. simvastatin (daily dose ≥ 40mg)
    - ii. atorvastatin (daily dose ≥ 20mg)
    - iii. rosuvastatin (daily dose ≥ 10mg)
  - b. Member has experienced ONE of the following:

- i. Rhabdomyolysis or muscle symptoms with creatine kinase (CK) elevations  $\geq 10$  times upper limit of normal (ULN) on any statin OR
- ii. Myalgia (muscle symptoms without CK elevations) or myositis (muscle symptoms with CK elevations  $< 10$  times ULN) with TWO statins

Authorization length for mipomersen sodium and lomitapide is 6 months.

**Re-authorization criteria:** Mipomersen sodium and lomitapide are re-approved when there is a reduction in LDL level of at least 25% since initiation of therapy with respective drug.

Alirocumab (Praluent®) is approved when BOTH of the following are met:

- A. Diagnosis of ONE of the following:
  - 1. Hyperlipidemia; or
  - 2. Atherosclerotic cardiovascular disease as diagnosed by either stress test, angiography, atherosclerotic event (e.g. MI, angina, stroke, claudication, carotid stenosis) or arterial intervention for atherosclerotic disease (e.g. coronary, peripheral, carotid)

**AND**

- B. ONE of the following:
    - 1. LDL-C 70 mg/dL or greater after a minimum 8-week trial of at least moderate-intensity statin therapy; OR
    - 2. Inability to tolerate statin therapy as documented by ONE of the following:
      - a. Member had rhabdomyolysis or symptoms with creatine kinase (CK) exceeding 10 times the upper limit of normal (ULN) on any statin; OR
      - b. ONE of the following with TWO statins:
        - i. Myalgia (no CK elevation); OR
        - ii. Myositis (CK less than 10 times ULN); OR
        - iii. Hepatotoxicity from statin use (increased AST/ALT exceeding 3 times ULN);
- OR
- c. Liver disease documented by Child Pugh A or worse OR AST/ALT exceeding 3 times ULN for at least 6 weeks

Evolocumab (Repatha®) is approved when BOTH of the following are met:

- A. Diagnosis of ONE of the following:
  - 1. Hyperlipidemia; or
  - 2. Homozygous familial hypercholesterolemia; or
  - 3. Atherosclerotic cardiovascular disease as diagnosed by either stress test, angiography, atherosclerotic event (e.g. MI, angina, stroke, claudication, carotid stenosis) or arterial intervention for atherosclerotic disease (e.g. coronary, peripheral, carotid)

**AND**

- B. ONE of the following:
    - 1. LDL-C 70 mg/dL or greater after a minimum 8-week trial of at least moderate-intensity statin therapy; OR
    - 2. Inability to tolerate statin therapy as documented by ONE of the following:
      - a. Member had rhabdomyolysis or symptoms with creatine kinase (CK) exceeding 10 times the upper limit of normal (ULN) on any statin; OR
      - b. ONE of the following with TWO statins:
        - i. Myalgia (no CK elevation); OR
        - ii. Myositis (CK less than 10 times ULN); OR
        - iii. Hepatotoxicity from statin use (increased AST/ALT exceeding 3 times ULN);
- OR

- c. Liver disease documented by Child Pugh A or worse OR AST/ALT exceeding 3 times ULN for at least 6 weeks

Authorization duration: 6 months

Continuation criteria: evolocumab (Repatha®) and alirocumab (Praluent®) are approved for continuation when there is a sustained reduction in LDL-C of at least 25% since initiation of therapy  
Authorization duration: 12 months

▶ **Black Box Warning:**

Risk of hepatotoxicity:

**Mipomersen and lomitapide** can cause elevations in transaminases. In clinical trials, 12% of patients treated with mipomersen and 34% of patients treated with lomitapide had at least 1 elevation in ALT or AST at least 3 times the upper limit of normal (ULN) or higher. There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), alkaline phosphatase or partial thromboplastin time (PTT).

Mipomersen and lomitapide also increase hepatic fat (hepatic steatosis), with or without concomitant increase in transaminases. In the trials of patients with heterozygous familial hypercholesterolemia and hyperlipidemia, the median absolute increase in hepatic fat was 10% (mipomersen) and 6% (lomitapide) after 26 weeks of treatment from 0% at baseline, measured by magnetic resonance imaging (MRI) and 1% at baseline, measured by magnetic resonance spectroscopy (MRS) respectively. Hepatic steatosis is a risk factor for advanced liver disease, including steatohepatitis and cirrhosis.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment, adjust the dose of lomitapide and withhold the dose of mipomersen if the ALT or AST are at least 3 times the ULN. Discontinue mipomersen and lomitapide for clinically significant liver toxicity.

Because of the risk of hepatotoxicity, mipomersen and lomitapide are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

▶ **Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

▶ **References:**

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#### ▾ Applicable Drugs:

 Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand name	Generic name
Kynamro®	Mipomersen Sodium
Juxtapid®	Lomitapide
Praluent®	alirocumab
Repatha®	evolocumab

#### ▾ Cross References:

N/A

<b>Policy Version Number:</b>	8.00
<b>P&amp;T Approval Date:</b>	January 10, 2019
<b>Policy Effective Date:</b>	April 01, 2019

**Next Required Review Date:**

January 10, 2020

The Policy Bulletins on this web site were developed to assist the Company in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Company, please refer to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Company does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of the Company. If you have a specific medical condition, please consult with your doctor. The Company reserves the right at any time to change or update its Policy Bulletins.