

Pharmacy Policy Bulletin

Title: Cholesterol Lowering Agents

Policy #: Rx.01.131

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®)**, **alirocumab (Praluent®)**, **evolocumab (Repatha®)**, **bempedoic acid (Nexletol™)**, and **bempedoic acid/ezetimibe (Nexlizet™)** 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).

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:

- To reduce the risk of myocardial infarction, stroke, coronary revascularization and unstable angina requiring hospitalization in adults with established cardiovascular disease.
- 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.
- 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.

Bempedoic acid (Nexleto™) is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid and its active metabolite, ESP15228, require coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA and ESP15228-CoA, respectively. ACSVL1 is expressed primarily in the liver. Inhibition of ACL by ETC-1002-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of low-density lipoprotein receptors.

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.

Bempedoic acid (Nexleto™) and bempedoic acid/ezetimibe (Nexlizet™) is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

Policy:

INITIAL CRITERIA: Lomitapide (Juxtapid®) is approved when documentation is provided of ALL of the following:

- A. Diagnosis of Homozygous Familial Hypercholesterolemia; and
- B. 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 LDL receptor adaptor protein 1 (i.e. LDLRAP1 or ARH), or
 - b. Untreated LDL-C > 500mg/dL or treated LDL cholesterol ≥ 300mg/dL with either of the following:
 - i. Cutaneous or tendinous xanthoma prior to 10 years of age, or
 - ii. Elevated LDL cholesterol prior to lipid-lowering therapy consistent with HeFH in both parents; AND
- C. ONE of the following:
 - a. Inadequate response to one of the following medications in combination with ezetimibe:
 - i. Simvastatin (daily doses ≥ 40mg); or
 - ii. Atorvastatin (daily doses ≥ 20mg); or
 - iii. Rosuvastatin (daily doses ≥ 10mg); OR
 - b. Member has experience ONE of the following:
 - i. Rhabdomyolysis or muscle symptoms with creatine kinase (CK) elevations > 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; AND
- D. Inadequate response or inability to tolerate evolocumab (Repatha®) or alirocumab (Praluent®); and
- E. Prescribed by or in consultation with one of the following:
 - a. Cardiologist; or
 - b. Endocrinologist; or
 - c. Lipid specialist

Initial authorization: 6 months

Re-authorization criteria: Lomitapide is re-approved when there is a reduction in LDL level of at least 25% since initiation of therapy.

Reauthorization: 12 months

INITIAL CRITERIA: Alirocumab (Praluent®) is approved when ALL 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 diseases (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 has 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 (increase 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; and
- C. One of the following:
 - 1. Member has been receiving a minimum of 8-week trial of ezetimibe (Zetia®) therapy as adjunct to maximally tolerated statin therapy; or
 - 2. Member has contraindication or inability to tolerate ezetimibe (Zetia®)

INITIAL CRITERIA: Evolocumab (Repatha®) is approved when ALL 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; and
- C. One of the following:
 - 1. Member has been receiving a minimum of 8-week trial of ezetimibe (Zetia®) therapy as adjunct to maximally tolerated statin therapy; or
 - 2. Member has contraindication or inability to tolerate ezetimibe (Zetia)

Initial Authorization: 6 months

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

Reauthorization: 12 months

INITIAL CRITERIA: Bempedoic acid (Nexletol™), bempedoic acid/ezetimibe (Nexlizet™) is approved when ALL of the following are met:

- A. One of the following diagnoses:

1. Heterozygous familial hypercholesterolemia (HeFH); or
 2. Atherosclerotic cardiovascular disease (ASCVD) as diagnosed by either stress test, angiography, atherosclerotic event (e.g. MI, angina, stroke, claudication, carotid stenosis) or arterial intervention for atherosclerotic diseases (e.g. coronary, peripheral, carotid); and
- B. One of the following:
1. LDL-C 70 mg/dL or greater after at least 8 consecutive weeks of one low-intensity, moderate-intensity or high-intensity statin therapy and member will continue to receive statin therapy at maximally tolerated dose; or
 2. Inability to tolerate statin therapy as documented by ONE of the following:
 - a. Member has 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 (increase 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; and
- C. ONE of the following:
1. Member has been receiving at least 8 consecutive weeks of ezetimibe (Zetia®) therapy as adjunct to maximally tolerated statin therapy; or
 2. Member has contraindication or intolerance to ezetimibe (Zetia®)

Initial Authorization: 6 months

REAUTHORIZATION CRITERIA: Bempedoic acid (Nexletol™), Bempedoic acid/ezetimibe (Nexlizet™) is approved when ALL of the following are met:

- A. Documentation of a sustained reduction of LDL-C by at least 17% from the time therapy began or sustained below 70mg/dL; and
- B. ONE of the following:
 1. Member continues to receive other lipid-lowering therapy (e.g., statins, ezetimibe) at the maximally tolerated dose; or
 2. Member has inability to tolerate other lipid-lowering therapy (e.g., statins, ezetimibe)

Reauthorization: 12 months

Black Box Warning as shown in the drug Prescribing Information:

Risk of hepatotoxicity:

Lomitapide (Juxtapid®) can cause elevations in transaminases. In clinical trials, % 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).

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 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 if the ALT or AST are at least 3 times the ULN. Discontinue lomitapide for clinically significant liver toxicity.

Because of the risk of hepatotoxicity, 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:

Farnier M, Bruckert E. Severe familial hypercholesterolemia: Current and future management. *Arch Cardiovasc Dis*. 2012 Dec; 105(12):656-65. Accessed July 21, 2021.

Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidology*. 2011;5:S1-S8. Accessed July 21, 2021.

Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110:227-39. Accessed July 21, 2021.

Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for the patient-centered management of dyslipidemia: Part 1- full report. *J Clin Lipidology*. 2015;9:129-69. Accessed July 21, 2021.

Juxtapid® (lomitapide) [prescribing information.] Cambridge, MA. Aegerion Pharmaceuticals. December 2019. Available at: <http://juxtapidpro.com/prescribing-information>. Accessed July 21, 2021.

Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. *Atherosclerosis*. 2012 Aug; 223(2):262-8. Accessed July 21, 2021.

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines. *Circulation*. 2013. Available from: http://circ.ahajournals.org/cgi/content/short/129/25_suppl_2/S1?rss=1&ssource=mfr. Accessed July 21, 2021.

Visser ME, Witztum JL, Stroes ES, et al. Antisense oligonucleotides for the treatment of dyslipidaemia. *Eur Heart J*. 2012 Jun; 33(12):1451-8. doi: 10.1093/eurheartj/ehs084. Epub 2012 May 24.

Lambert G, Sjouke B, Choque B, Kastelein JJP, Hovingh GK. The PCSK9 decade. *J Lipid Res*. 2012; 53(12): 2515-24. DOI: 10.1194/jlr.R026658. Accessed July 21, 2021.

Farnier M. PCSK9: From discovery to therapeutic applications. *Arch Cardiovascular Dis*. 2014; 107: 58-66. DOI: 10.1016/j.acvd.2013.10.007. Accessed July 21, 2021.

Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidology*. 2011;5:S1-S8. Accessed July 21, 2021.

Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for the patient-centered management of dyslipidemia: Part 1- full report. *J Clin Lipidology*. 2015;9:129-69. Accessed July 21, 2021.

Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly Jr DD, DePalma SM, Minissian, MB, Orringer CE, Smith Jr SC, 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Exper Decision Consensus Pathways. *Journal of the American College of Cardiology* (2017), doi: 10.1016/j.jacc.2017.07.745. Accessed July 21, 2021.

Nexletol™ (bempedoic acid) [prescribing information]. Ann Arbor, MI: Esperion Therapeutics, Inc.; February 2020. Available from: <https://pi.esperion.com/nexletol/nexletol-pi.pdf>. Accessed July 21, 2021.

Nexlizet™ (bempedoic acid and ezetimibe) [prescribing information]. Ann Arbor, MI: Esperion Therapeutics, Inc.; February 2020. Available from: <https://pi.esperion.com/nexlizet/nexlizet-pi.pdf>. Accessed July 21, 2021.

Praluent® (alirocumab) [package insert]. Bridgewater, NJ. Sanofi-Aventis US LLC. April 2021. Available from: <http://products.sanofi.us/praluent/praluent.pdf>. Accessed July 21, 2021.

Repatha® (evolocumab) [package insert]. Thousand Oaks, CA. Amgen Inc. February 2021. Available from: https://www.pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/repatha/repatha_pi_hcp_english.pdf. Accessed July 21, 2021.

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines. Circulation. 2013. <https://doi.org/10.1161/01.cir.0000437738.63853.7a>. Accessed July 21, 2021.

Varghese MJ. Familial hypercholesterolemia: a review. Ann Pediatr Cardiol. 2014;7:107-17. Accessed July 21, 2021.

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
Juxtapid®	Lomitapide
Praluent®	alirocumab
Repatha®	evolocumab
Nexletol™	Bempedoic acid
Nexlizet™	Bempedoic acid/ezetimibe

Cross References:

Off-Label Use Rx.01.33

Policy Version Number:	12.00
P&T Approval Date:	June 10, 2021
Policy Effective Date:	October 01, 2021
Next Required Review Date:	June 10, 2022

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.
