Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 12/12/2024

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Leqvio® (inclisiran)

HCPCS: J1306

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indications
   b. FDA approved age
   c. Trial and therapeutic failure with one high-intensity statin
      OR
   d. History of statin-associated side effects or intolerance (e.g., skeletal muscle related symptoms) after a trial of two generic statins
      OR
   e. History of rhabdomyolysis after a trial of one statin
   f. Not to be used in combination with other PCSK9 inhibitors
   g. Trial and failure, contraindication, or intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list and/or BCBSM/BCN's prior authorization and step therapy documents

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein that targets LDL receptors for degradation and reduces the liver's ability to remove circulating LDL from the blood. Elevated levels of circulating PCSK9 are associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) and consequently worsened cardiovascular outcomes. Inhibitors of PCSK9 bind to circulating PCSK9 and prevent it from binding to and degrading LDL receptors on the liver surface, resulting in more LDL receptors to remove circulating LDL from the blood.

- The first two fully human monoclonal antibodies to PCSK9 to have been approved by the FDA to treat patients with inadequately treated levels of LDL-C were Repatha (evolocumab) and Praluent (alirocumab). Both work by binding to circulating PCSK9 and preventing it from binding to and degrading LDL receptors on the liver surface, resulting in more LDL receptors to remove circulating LDL from the blood. Praluent and Repatha have been shown to lower LDL-C by up to 60% in patients on concurrent statin therapy and additionally have demonstrated cardiovascular outcomes benefits. Both products are approved for the following indications:

    - Secondary prevention of cardiovascular events (e.g., stroke, myocardial infarction, unstable angina) in adults with established cardiovascular disease

    - As an adjunct to diet, alone or in combination with other LDL-C lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C

        - Repatha is also approved for pediatric patients 10 years of age and older with HeFH, and Praluent for pediatric patients 8 years of age and older with HeFH, as an adjunct to diet and other LDL-C-lowering therapies

    - As an adjunct to other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C

        - Praluent is indicated for adults with HoFH, whereas Repatha has established safety and effectiveness in patients 10 years of age and older with HoFH.

- The most recent addition to the PCSK9 inhibitor class is Leqvio (inclisiran), a small interfering RNA (siRNA) directed to PCSK9 mRNA. Leqvio is the first siRNA therapy approved for LDL-C reduction. It has been approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C.

- Unlike Praluent and Repatha, Leqvio utilizes the RNA interference mechanism to inhibit hepatic synthesis of PCSK9. In doing so, LDL receptor recycling and expression on the liver surface increase, thereby increasing LDL-C uptake by hepatocytes and consequently lowering the levels in circulation. In clinical trials Leqvio has demonstrated comparable LDL-C lowering potency to Praluent and Repatha. Leqvio's effect on cardiovascular outcomes has yet to be determined. The ORION-4 and CITORION-2P cardiovascular outcomes trials with Leqvio are underway and expected to be completed in 2026 and 2027, respectively; results are expected to be comparable to Praluent and Repatha

- All three products are administered as subcutaneous injections. With regard to administration and dosing frequency Praluent and Repatha are similar; both products can be self-administered and are dosed every two weeks or every month. Leqvio, however, is intended for administration by a healthcare professional only and is administered every six months after an initial dose titration. Less frequent dosing and a required office visit could potentially yield better adherence with Leqvio compared to Praluent and Repatha.

- Combination use of more than one PCSK9 inhibitor has not been evaluated, and in clinical trials for Leqvio patients who were taking Praluent and/or Repatha were excluded from participating. Therefore, the use of any of the PCSK9 inhibitors in combination is not supported by evidence.

- The American College of Cardiology (ACC) at present in their 2022 Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering prefers PCSK9 monoclonal antibodies (i.e., Repatha, Praluent) as the initial PCSK9 inhibitor of choice in light of the demonstrated efficacy, safety, and cardiovascular outcomes benefits seen in the FOURIER and ODYSSEY Outcomes trials; however, those with poor adherence to PCSK9 monoclonal antibodies, adverse effects from PCSK9 monoclonal antibodies, or those unable to self-inject may be considered for use of Leqvio. Use of the product(s) with the lowest net cost provides the greatest value.

- Patients with clinical ASCVD include those with a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD (including aortic aneurysm), all of atherosclerotic origin. These patients with established cardiovascular disease are at high risk of a cardiovascular disease event. Those with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (i.e. age $\geq$ 65 years old, HeFH, diabetes mellitus, hypertension, chronic kidney disease, current smoking, LDL-C $\geq$ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe, history of congestive heart failure, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)) are considered very-high risk for future ASCVD events. Therapy to reduce the risk of subsequent events is known as secondary prevention.

- Patients presenting with severe primary hypercholesterolemia (LDL $\geq$ 190 mg/dL), including those with familial hypercholesterolemia (FH), have a high risk of ASCVD and premature/recurrent coronary events. Regardless of whether LDL-C levels $\geq$ 190 mg/dL are found to have a genetic mutation associated with FH, those patients with very high LDL-C are most likely to achieve the greatest benefit both in LDL-C reduction and ASCVD risk reduction from evidence based LDL-C-Lowering therapy.

- FH is an autosomal dominant genetic disease caused by functional mutations in the LDLR, APOB, or PCSK9 genes, and is characterized by lifelong elevations of LDL-C that if left untreated leads to early-onset atherosclerosis and risk of cardiovascular events. Mutations in the LDLR gene are the most common causes of FH, accounting for 85%-90% of genetically confirmed cases. Diagnosis of FH should be considered in children presenting with persistently elevated LDL-C > 160 mg/dL, adults with LDL-C >190 mg/dL, and in all patients with early coronary artery disease. In the absence of confirmatory genetic testing, FH can be diagnosed using clinical criteria; commonly used diagnostic tools for the diagnosis of FH include the US Make Early Diagnosis to Prevent early Death (MEDPED) criteria, the UK Simon Broome system, and the Dutch Lipid Clinic Network criteria. Though the tools differ from one another, their predictive values are comparable.

- The incidence of HeFH in the United States is approximately 1 in 500. The Dutch Lipid Clinic Network criteria provide the most detailed assessment of the likelihood of a diagnosis of HeFH and includes the following parameters to confirm diagnosis:

    - An untreated LDL of $\geq$ 190 mg/dL (or $\geq$ 160 mg/dL in patients under 16 years of age) and at least one of the following:

        - Family history of a first or second degree relative with FH.

        - Family history of tendinous xanthoma(s) in 1st or 2nd degree relative and/or arcus cornealis in 1st degree relative

        - History of 1st degree relative with known premature coronary and vascular disease (i.e., < 55 years old in men, and < 60 years old in women)

  - Physical signs of FH such as the presence of tendon xanthomas in the patient, premature corneal arcus, premature tuberous xanthomas, or premature xanthelasma.

  - Presence of a mutation causing FH by DNA testing (e.g. mutation in LDLR, APOB, PCSK9).

- The UK Simon Broome System criteria differs from the Dutch Lipid Clinic Network in that the presence of a positive genetic test alone is sufficient to definitively diagnose familial hypercholesterolemia. Additional parameters to aid in the diagnosis of HeFH under the Simon Broome system include an LDL > 190 mg/dL and at least one of the following:

  - Tendon xanthoma in the patient or a 1st or 2nd degree relative

  - Presence of mutations in the LDLR, APOB, or PCSK9 gene

  - Family history of MI in a 2nd degree relative under 50 years old or a 1st degree relative under 60 years old

  - Family history of total cholesterol > 290 mg/dL in a 1st or 2nd degree relative.

- HoFH is ultra-rare affecting approximately 1,300 patients in the United States. Genetic mutations primarily affect the LDLR gene, resulting in virtually absent or impaired receptor-mediated catabolism of LDL-C and leading to severely elevated LDL-C levels (> 400 mg/dL) and a lack of responsiveness to standard lipid-lowering therapies. Diagnosis can be made via genetic testing for causative mutations in the LRLR, APOB, and PCSK9 genes, or clinically in patients with an untreated LDL-C of >500 mg/dL (or treated LDL-C $\geq$ 300 mg/dL) and one of the following: cutaneous or tendon xanthoma prior to 10 years of age, or elevated LDL-C levels in both parents consistent with HeFH. Untreated LDL-C < 500 mg/dL may be present in some patients with HoFH, particularly in young children, and would warrant genetic testing to clarify or confirm diagnosis. More recently, a rare autosomal recessive form of FH has been identified that is caused by mutations in the LDLRAP1 (also known as the ARH) gene. Though coined autosomal recessive hypercholesterolemia, this condition is considered as a form of HoFH and should be treated as such.

- LDL-C is a primary cause of atherosclerosis and a major risk factor for ASCVD. Randomized controlled trials of cholesterol lowering therapies have consistently demonstrated that LDL-C lowering reduces the risk of ASCVD. Generally speaking, lowering LDL-C levels by 1% yields an approximately 1% reduction in ASCVD risk, though this percent risk reduction may be slightly more or less at higher and lower baseline LDL-C levels, respectively.

- Statins are the cornerstone of pharmacologic therapy for lowering LDL-C both as primary and secondary ASCVD prevention. Statin therapy is divided into three categories by intensity, with atorvastatin, rosuvastatin, and simvastatin being the primary statin medications used in clinical practice.

	High Intensity	Moderate Intensity	Low Intensity
LDL-C Lowering	≥ 50%	30-49%	<30%
Statins**	Atorvastatin° 40mg, 80mg Rosuvastatin* 20mg, 40mg	Atorvastatin° 10mg, 20mg Rosuvastatin* 5mg, 10mg Simvastatin° 20-40mg Pravastatin* 40mg, 80mg Lovastatin° 40mg, 80mg Fluvastatin° XL 80mg Fluvastatin° 40mg BID Pitavastatin° 1-4mg	Simvastatin° 10mg Pravastatin* 10-20mg Lovastatin° 20mg Fluvastatin° 20-40mg

*Hydrophilic statin
°Lipophilic statin
**Hydrophilic statins have greater hepatoselectivity and less influence on smooth muscle proliferation than lipophilic statins, which diffuse nonselectively into extrahepatic tissues such as the muscle and may therefore be more likely to cause myopathy.

- The 2018 American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines for the management of high cholesterol recommend initiating treatment with healthy lifestyle modifications and a high-intensity or maximally tolerated statin to lower LDL-C by ≥ 50% to a goal LDL-C level of <70 mg/dL for secondary prevention of ASCVD or <100 mg/dL for severe hypercholesterolemia, including FH. Treatment with high-intensity or maximally tolerated statins has demonstrated reduced ASCVD risk in both primary and secondary prevention trials, in addition to reduced risk of myocardial infarction, coronary heart disease, and all-cause death with phenotypically or genetically confirmed FH. Peak changes in LDL-C levels are generally seen between 4 and 12 weeks after initiating therapy.

- If with a high-intensity statin the patient experiences statin-associated side effects that are not severe (e.g., myalgias), the statin dose can be reduced or alternate statins can be trialed with the ultimate goal of treating with a guideline-recommended maximally tolerated statin.

    - There are a variety of generically available statins that can be dosed at different intensities or dosing regimens to help mitigate bothersome side effects; therefore, it is reasonable to require a trial of at least two statins in patients experiencing statin-associated side effects.

    - Patients who experience more severe side effects with statin therapy (e.g. rhabdomyolysis) or recurrent statin-associated muscle symptoms despite multiple statin rechallenge attempts may need to discontinue statin use and transition to non-statin therapy that has been shown to provide clinical benefit.

- If maximally tolerated statin therapy fails to reduce LDL-C by at least 50% and/or the LDL-C level remains above goal, the 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-C lowering recommends considering adding either ezetimibe or a PCSK9 monoclonal antibody as the initial non-statin therapy. Preference of which agent to add may be influenced by the desired amount of LDL-C-lowering. ACC/AHA guidelines suggest that additional ASCVD risk reduction can be derived by adding ezetimibe to statin therapy, which can lower LDL-C by an additional 13-20%, and placebo-controlled randomized clinical trials have demonstrated favorable safety profiles and additional LDL-C reduction ranging from 43-64% with PCSK9 inhibitors in patients on maximally tolerated statin therapy. If additional LDL-C lowering is required after addition of a single nonstatin agent (ezetimibe or PCSK9 monoclonal antibody) to statin therapy, a second evidence-based non-statin agent should be considered (e.g., ezetimibe + PCSK9 monoclonal antibody).

- If additional LDL-C lowering is warranted despite maximally tolerated statin therapy, ezetimibe, and a PSK9 monoclonal antibody, the addition of bempedoic acid may be considered, or the PCSK9 monoclonal antibody may be replaced with inclisiran. There is no cardiovascular outcomes data available at this time for either bempedoic acid or inclisiran. For persistent severe hypercholesterolemia where drug therapy fails to adequately control LDL-C, such as

in the case of HoFH, specialized therapies such as evinacumab, lomitapide, or LDL apheresis may be necessary to control LDL-C and referral to a lipid specialist may be indicated. Of note, the safety and efficacy of the concurrent use of lomitapide with PCSK9 inhibitors like Repatha and Praluent for the treatment of HoFH has not been established.

- For children and adolescents 10 years of age and older with an LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with a clinical presentation consistent with FH who fail to respond adequately to 3 to 6 months of lifestyle therapy, the 2018 guidelines suggest initiation of statin therapy. Statin treatment intensity in children is not specified in the guidelines as it should be individualized to the child based on the severity of hypercholesterolemia and the needs of the child/family. Use of non-statin therapies to further treat persistently elevated LDL-C in children is not addressed in the guidelines; however, for children with HoFH Repatha may be a reasonable next step for children and adolescents who require additional LDL-C lowering since it is approved by the FDA for use in pediatric patients 10 years of age and older with HoFH in combination with diet and other LDL-C lowering therapies. Praluent, however, is only approved for adult patients with HoFH.

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14. Cuchel M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. European Heart Journal (2023) 44, 2277-2291. https://doi.org/10.1093/eurheartj/ehad197

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<tr><td>1.6</td><td>Effective Date: 12/14/2023</td><td>Annual review of criteria performed; no changes were made</td></tr>
<tr><td>1.5</td><td>Effective Date: 12/01/2022</td><td>Added criteria preventing use of PCSK9 inhibitors in combination with one another</td></tr>
<tr><td>1.4</td><td>Effective Date: 06/09/2022</td><td>Removed criteria requiring trial and failure of Repatha or Praluent for Leqvio;will utilize trial and failure of preferred criteria (bullet f) instead for flexibility</td></tr>
<tr><td>1.3</td><td>Effective Date: 03/01/2022</td><td>Removed criteria requiring t/f of Repatha or Praluent for Leqvio;will utilize t/f of preferred criteria (bullet f) instead for flexibility</td></tr>
<tr><td>1.2</td><td>Effective Date: 03/01/2022</td><td>UM medical management system update for MAPPO and BCNA
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*