# inclisiran (Leqvio®)

**Medicare Advantage Medical Policy #MA-246**
Original Effective Date: 01/01/2027
Current Effective Date: 01/01/2027

*Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Blue Advantage does not cover investigational or experimental services, including any drug, device, procedure, or service provided under the investigational arm of a clinical trial or study unless mandated by the Centers for Medicare and Medicaid Services. Coverage is limited to routine services for Category A IDE studies and to devices and related services for Category B IDE studies when not supplied by the trial sponsor. Approved IDE studies are posted on www.cms.gov/medicare/coverage/evidence.*

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider inclisiran (Leqvio®) ‡ in patients with familial hypercholesterolemia, hypercholesterolemia, or atherosclerotic cardiovascular disease to be **eligible for coverage.****

Patient Selection Criteria

**Initial:**

Coverage eligibility will be considered for inclisiran (Leqvio) when the following criteria are met (I, II, III, IV, V, VI, **and** VII):

I. Patient is 18 years of age or older (EXCEPT in HoFH where the age is 12-17 years of age and in HeFH where the age is 12 years of age or older); AND
II. Patient is adherent to any medications required for therapy prior to receiving authorization for inclisiran (Leqvio); AND
III. inclisiran (Leqvio) will NOT be used in combination with lomitapide (Juxtapid®)‡, evolocumab (Repatha™)‡, alirocumab (Praluent®)‡, evinacumab-dgnb (Evkeeza™)‡, or lerodalcibep-liga (Lerochol™)‡ ; AND
IV. inclisiran (Leqvio) will be used along with a maximally tolerated statin [in those who are not considered statin intolerant (see below for statin intolerance)]; AND
V. inclisiran (Leqvio) is dosed as 284 mg given initially, at 3 months, and then every 6 months thereafter; AND
VI. Patient must meet ONE of the following (A, B, C, D, E, F, **or** G):
    A. Patient has a diagnosis of Familial Hypercholesterolemia (FH) withOUT clinical atherosclerotic cardiovascular disease, defined as a WHO (World Health Organization)/Dutch Lipid Clinic Network score of greater than 8; AND
        i. Patient's low density lipoprotein cholesterol (LDL-C) is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 70 mg/dL for the patient's clinical risk category) with a high-intensity statin [rosuvastatin

(Crestor®)‡ 20-40 mg, atorvastatin (Lipitor®)‡ 40-80 mg] for at least 3 months; OR

ii. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 70 mg/dL for the patient's clinical risk category) with a maximally tolerated stable daily statin (of any potency) for at least 3 months ONLY if proof is given that a high-intensity statin was not well tolerated; OR

B. Patient has a diagnosis of FH withOUT clinical atherosclerotic cardiovascular disease, defined as a WHO/Dutch Lipid Clinic Network score of greater than 8; AND
   i. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 70 mg/dL for the patient's clinical risk category) due to statin intolerance; AND
   ii. Patient meets ALL of the following criteria confirming statin intolerant:
      1. Patient was unable to tolerate at least 2 different statins. [The inability to tolerate one statin will be accepted if the patient experienced rhabdomyolysis or clinically-significant myonecrosis secondary to a statin. Rhabdomyolysis/myonecrosis is considered to be a muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness ALONG WITH either: a.) acute renal failure or myoglobinuria AND elevated creatine kinase levels (i.e., greater than or equal to 10 times the upper limit of normal) OR b.) elevated creatine kinase levels (i.e., greater than or equal to 10 times the upper limit of normal) alone]; AND
      2. Patient's intolerance was associated with confirmed, intolerable statin-related adverse effects [i.e., skeletal related muscle symptoms (myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness])]; AND
      3. Patient's symptoms or biomarker changes resolved or showed significant improvement on dose decrease or discontinuation; OR

C. Patient has the presence of clinical atherosclerotic cardiovascular disease (either FH or non-FH); AND
   i. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 55 mg/dL for very high-risk individuals or less than 70 mg/dL for high-risk individuals) with a high-intensity statin [rosuvastatin (Crestor) 20-40 mg, atorvastatin (Lipitor) 40-80 mg] for at least 3 months; OR
   ii. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 55 mg/dL for very high-risk individuals or less than 70 mg/dL for high-risk individuals) with a maximally tolerated stable daily statin (of any potency) for at least 3-months ONLY if proof is given that a high-intensity statin was not well tolerated; OR

D. Patient has the presence of clinical atherosclerotic cardiovascular disease (either FH or non-FH); AND

i. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 55 mg/dL for very high-risk individuals or less than 70 mg/dL for high-risk individuals) due to statin intolerance; AND
ii. Patient meets ALL of the following criteria confirming statin intolerance:
1. Patient was unable to tolerate at least 2 different statins. [The inability to tolerate one statin will be accepted if the patient experienced rhabdomyolysis or clinically significant myonecrosis secondary to a statin. Rhabdomyolysis/myonecrosis is considered to be a muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness ALONG WITH either: a.) acute renal failure or myoglobinuria AND elevated creatine kinase levels (i.e., greater than or equal to 10 times the upper limit of normal) OR b.) elevated creatine kinase levels (i.e., greater than or equal to 10 times the upper limit of normal) alone]; AND
2. Patient's intolerance was associated with confirmed, intolerable statin-related adverse effects [i.e., skeletal related muscle symptoms (myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness])]; AND
3. Patient's symptoms or biomarker changes resolved or showed significant improvement on dose decrease or discontinuation; AND

E. Patient has hypercholesterolemia (NOT associated with FH or clinical ASCVD); AND
i. Patient has a baseline (untreated) LDL-C greater than or equal to 190 mg/dL; AND
ii. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 100 mg/dL for the patient's clinical risk category) with a high-intensity statin (rosuvastatin [Crestor] 20-40 mg, atorvastatin [Lipitor] 40-80 mg) PLUS ezetimibe (Zetia®)‡ 10 mg daily for at least 3 months; OR
iii. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 100 mg/dL for the patient's clinical risk category) with a maximally tolerated stable daily statin (of any potency) PLUS ezetimibe (Zetia) 10 mg daily for at least 3 months ONLY if proof is given that a high-intensity statin was not well tolerated; OR

F. Patient has hypercholesterolemia (not associated with FH or clinical ASCVD); AND
i. Patient has a baseline (untreated) LDL-C greater than or equal to 190 mg/dL; AND
ii. Patient's LDL-C is not adequately controlled (i.e., not at the LDL-C treatment goal of less than 100 mg/dL for the patient's clinical risk category) due to statin intolerance; AND
iii. Patient must meet ALL of the following criteria for statin intolerance:
1. Patient was unable to tolerate at least 2 different statins. (The inability to tolerate one statin will be accepted if the patient experienced rhabdomyolysis or clinically significant myonecrosis secondary to a

statin. Rhabdomyolysis/myonecrosis is considered to be a muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness ALONG WITH either: a.) acute renal failure or myoglobinuria AND elevated creatine kinase levels [i.e., greater than or equal to 10 times the upper limit of normal] OR b.) elevated creatine kinase levels [i.e., greater than or equal to 10 times the upper limit of normal] alone); AND

2. Patient's intolerance was associated with confirmed, intolerable statin-related adverse effects (i.e., skeletal related muscle symptoms [myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness)]); AND
3. Patient's symptoms or biomarker changes resolved or showed significant improvement on dose decrease or discontinuation; OR

G. Patient meets ONE of the following (i, ii, **or** iii)

i. Patient has had genetic confirmation of two pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR

ii. Patient has an untreated LDL-C level greater than 400 mg/dL AND meets ONE of the following (1 **or** 2):
*(Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.)*

1. Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR
*(Note: Clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.)*
2. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); OR
*(Note: An example of HeFH in both parents would be if both had an untreated LDL-C level greater than or equal to 190 mg/dL and/or an untreated total cholesterol level greater than 250 mg/dL)*
*(Note: In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH)*

iii. Patient has a treated LDL-C level greater than or equal to 300 mg/dL AND meets ONE of the following (1 **or** 2):
*(Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins [e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin], ezetimibe, a PCSK9 inhibitor [e.g., Praluent (alirocumab subcutaneous injection)], Evkeeza [evinacumab-dgnb intravenous infusion], or Juxtapid [lomitapide capsules])*

1. Patient had clinical manifestations of HoFH before the age of 10 years; OR
   *(Note: Examples of clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.)*
2. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with HeFH; AND
   *(Note: An example of HeFH in both parents would be if both had an untreated LDL-C greater than or equal to 190 mg/dL and/or an untreated total cholesterol greater than 250 mg/dL.)*
   *(Note: In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH)*

VII. Patient meets one of the following criteria (A **or** B):
   A. Patient meets both of the following criteria (i **and** ii):
      i. Patient has tried a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for greater than or equal to 12 continuous weeks at the FDA approved maximum dose for the requested indication; AND
      *(Note: Examples of PCSK9 inhibitors at their maximum dose for the same conditions as Leqvio include Repatha (evolocumab)140 mg once every 2 weeks or 420 mg once every 4 weeks and Praluent (alirocumab) 150 mg once every 2 weeks or 300 mg once every 4 weeks)*
      ii. Patient's LDL-C level after the max PCSK9 inhibitor dosing regimen remains above the applicable LDL-C treatment goal listed in the patient selection criteria above for the requested indication; OR
   B. Patient is known to have two LDL-receptor negative alleles.

**Continuation**: (Patient must meet I, II, III, **and** IV)

I. Patient has received an initial authorization from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
II. inclisiran (Leqvio) is dosed as 284 mg every 6 months; AND
III. inclisiran (Leqvio) will NOT be used in combination with lomitapide (Juxtapid), evolocumab (Repatha), alirocumab (Praluent), evinacumab-dgnb (Evkeeza), or lerodalcibep-liga (Lerochol); AND
IV. Patient has achieved clinically significant LDL-C lowering AND is adherent to inclisiran (Leqvio).

# When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of inclisiran (Leqvio) when the member has NOT tried statin therapy PLUS ezetimibe (Zetia) 10 mg daily OR does not meet the criteria for statin intolerance to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of inclisiran (Leqvio) when the patient has NOT tried and failed the required pre-requisite medications for a timeframe of at least 3 months to be **not medically necessary.****

Based on review of available data, the Health Plan considers the continued use of inclisiran (Leqvio) when the patient has NOT achieved clinically significant LDL-C lowering OR is NOT adherent to inclisiran (Leqvio) to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of inclisiran (Leqvio) when the patient has NOT tried and failed 12 weeks of therapy with a PCSK9 inhibitor (e.g., Repatha, Praluent) to be **not medically necessary.****

# When Services Are Considered Investigational

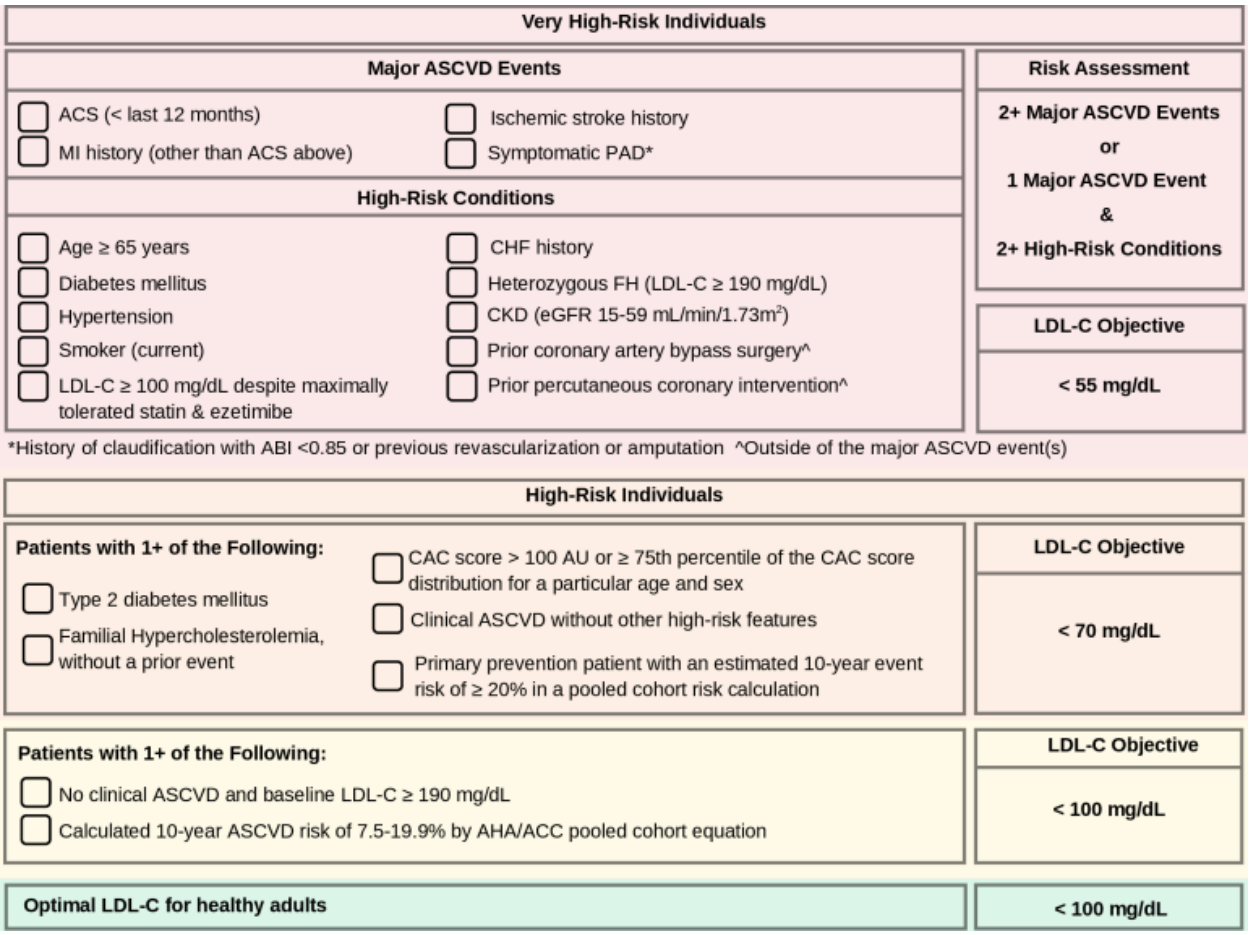
*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Health Plan considers the use of inclisiran (Leqvio) when patient selection criteria are not met (except those listed above as **not medically necessary****) to be **investigational.***

# Policy Guidelines

The 2026 ACC/AHA/Multisociety Guideline on the Management of Dyslipidemia retires and replaces the 2018 ACC/AHA Guideline on the Management of Blood Cholesterol. A key difference from the 2018 guideline is the return of defined LDL-C treatment goals. The 2018 guideline emphasized statin intensity, percentage LDL-C reduction, and LDL-C thresholds for considering additional therapy, rather than assigning specific LDL-C goals by risk category. In contrast, the 2026 guideline provides a more goal-directed, lifelong, risk-basked approach to lipid evaluation and treatment, with lower LDL-C goals for patients at higher ASCVD risk. Key updates also include expanded guidance across primary, secondary, and primordial prevention; routine lipid screening; lifestyle optimization; and earlier intensification of lipid-lowering therapy when LDL-C remains above goal.

The updated guidance supports lower LDL-C treatment goals based on ASCVD risk. In general, an LDL-C goal of less than 55 mg/dL is recommended for very high-risk patients, including those with clinical ASCVD at very high risk or marked subclinical atherosclerosis. An LDL-C goal of less than 70 mg/dL is recommended for high-risk patients, including those with clinical ASCVD not at very high risk, certain higher-risk primary prevention patients, and patients with subclinical atherosclerosis based on coronary artery calcium burden. For primary prevention patients with an LDL-C greater than or equal to 190mg/dL, a goal of less than 100 mg/dL is generally recommended, although a lower goal of less than 70 mg/dL may be appropriate when additional risk factors are present. The NLA graphic below provides additional detail on risk stratification and LDL-C goal selection.




The above figure comes from Nation Lipid Association 2025. Available at: https://www.lipid.org/wp-content/uploads/LDL-Cholesterol-Management-Simplified-09_08_2025-1.pdf.

**Clinical ASCVD (includes one or more of the following):**

I. Myocardial infarction or other acute coronary syndrome
II. Angina (stable or unstable)
III. Coronary or other revascularization procedure
IV. Transient ischemic attack
V. Ischemic stroke
VI. Atherosclerotic peripheral arterial disease (ABI of less than 0.90)
VII. Other documented atherosclerotic diseases such as
    A. Clinically significant coronary atherosclerosis diagnosed by coronary angiography, stress test, stress echocardiography, or myocardial perfusion imaging
    B. Renal atherosclerosis
    C. Aortic aneurysm secondary to atherosclerosis
    D. Carotid plaque (greater than or equal to 50% stenosis)

Primary hyperlipidemia is defined as an elevated LDL-C that is not due to a secondary cause. For the purpose of this policy, this condition is not associated with established cardiovascular disease, heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH). It may also be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated LDL-C levels.

# Background/Overview

Leqvio is a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA indicated as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, adults and pediatric patients aged 12 years and older with heterozygous familial hypercholesterolemia, and pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia. In hepatocytes, Leqvio utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation. Leqvio's dosage is 284 mg administered as a subcutaneous injection initially, again at 3 months, and then every 6 months. Leqvio should be administered by a healthcare professional.

It should be noted that the effects of Leqvio on cardiovascular morbidity and mortality have not been determined. Leqvio and the PCSK9 inhibitors have not been studied head to head, but have similar LDL-C reductions. Currently, the PCSK9 inhibitors offer an equally efficacious and more cost-effective option for the lowering of cholesterol in patients with HeFH or atherosclerotic cardiovascular disease.

**Hypercholesterolemia/Treatment Guidelines**

Approximately 30% of the United States population has elevated LDL-C (low density lipoprotein cholesterol). There is also a subset of hypercholesterolemia, known as familial hypercholesterolemia, which can affect nearly 1 in 300 individuals. Familial hypercholesterolemia can further be broken down into homozygous and heterozygous forms of familial hypercholesterolemia. The homozygous form is by far the rarest with an estimated incidence of 1 in 1,000,000 individuals. The gold standard for the treatment of elevated LDL-C levels is a statin given along with ezetimibe (Zetia) to provide the greatest amount of LDL-C lowering. Statin products also have proven cardiovascular outcomes.

Genetic testing is available to determine whether or not an individual has familial hypercholesterolemia, however clinical signs/symptoms are often a more practical method of diagnosing this condition. Clinical studies have used the WHO/Dutch Lipid Clinic Network Familial Hypercholesterolemia diagnostic criteria to determine if an individual had familial hypercholesterolemia. A score of > 8 is representative of "definite" familial hypercholesterolemia. The criteria are located in the following chart:

**WHO (World Health Organization)/Dutch Lipid Clinic Network Familial Hypercholesterolemia Criteria**

| | Points |
|---|---|
| Criteria<br>**Family history** | |
| First-degree relative with known premature* coronary and vascular disease, OR<br>First-degree relative with known LDL-C level above the 95th percentile | 1 |
| First-degree relative with tendinous xanthomata and/or arcus cornealis, OR<br>Children aged less than 18 years with LDL-C level above the 95th percentile | 2 |
| **Clinical history** | |
| Patient with premature* coronary artery disease | 2 |
| Patient with premature* cerebral or peripheral vascular disease | 1 |
| **Physical examination** | |
| Tendinous xanthomata | 6 |
| Arcus cornealis prior to age 45 years | 4 |
| **Cholesterol levels mg/dl (mmol/liter)** | |
| LDL-C >= 330 mg/dL ( ≥8.5) | 8 |
| LDL-C 250 – 329 mg/dL (6.5–8.4) | 5 |
| LDL-C 190 – 249 mg/dL (5.0–6.4) | 3 |
| LDL-C 155 – 189 mg/dL (4.0–4.9) | 1 |
| **DNA analysis** | |
| Functional mutation in the *LDLR, apo B or PCSK9* gene | 8 |
| **Diagnosis (diagnosis is based on the total number of points obtained)** | |
| Definite Familial Hypercholesterolemia | >8 |
| Probable Familial Hypercholesterolemia | 6 – 8 |
| Possible Familial Hypercholesterolemia | 3 – 5 |
| Unlikely Familial Hypercholesterolemia | <3 |

Premature = < 55 years in men; < 60 years in women

The 95th percentile in the "WHO/Dutch Lipid Clinic Network Familial Hypercholesterolemia Criteria" chart refers to the following LDL cholesterol values:

| Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|
| **Age (yr)** | **5th Percentile (LDL-C, mg/dL)** | **75th Percentile (LDL-C, mg/dL)** | **95th percentile (LDL-C, mg/dL)** | **Age (yr)** | **5th Percentile (LDL-C, mg/dL)** | **75th Percentile (LDL-C, mg/dL)** | **95th Percentile (LDL-C, mg/dL)** |
| 0–19 | 65 | 105 | 130 | 0–19 | 65 | 110 | 140 |
| 20–24 | 65 | 120 | 145 | 20–24 | 55 | 120 | 160 |
| 25–29 | 70 | 140 | 165 | 25–34 | 70 | 125 | 160 |
| 30–34 | 80 | 145 | 185 | 35–39 | 75 | 140 | 170 |
| 35–39 | 80 | 155 | 190 | 40–44 | 75 | 145 | 175 |
| 40–44 | 85 | 155 | 185 | 45–49 | 80 | 150 | 185 |
| 45–69 | 90 | 165 | 205 | 50–54 | 90 | 160 | 200 |
| 70 + | 90 | 165 | 185 | 55 + | 95 | 170 | 215 |

The above chart comes from Lipid Research Clinic Data 1983. Available at: http://www.ncbi.nlm.nih.gov/books/NBK351/table/A968/?report=objectonly.

The following link for the ATP III- A distribution of LDL Cholesterol in the US Adult Population also provides percentile values. It is located at:
http://circ.ahajournals.org/content/106/25/3237/T2.expansion.html.

**Primary Hypercholesterolemia/Clinical Atherosclerotic Cardiovascular Disease**

Primary hyperlipidemia is characterized by elevated levels of cholesterol or other lipids in the blood that are not secondary to another underlying condition. According to the 2022 American College of Cardiology (ACC) Expert Consensus Decision Pathway, this condition typically involves increased low-density lipoprotein cholesterol (LDL-C) and represents a significant risk factor for atherosclerotic cardiovascular disease (ASCVD).

Clinical ASCVD is defined as those with ACS or history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke or transient ischemic attack, or peripheral artery disease

(PAD) presumed to be of atherosclerotic origin. Subclinical atherosclerosis is defined in this document as significant atherosclerotic plaque observed in an asymptomatic patient on any of the following diagnostic studies: coronary artery calcification noted on computed tomography (CT) studies, including calcium scoring, cardiac CT coronary angiography, chest CT for ruling out pulmonary embolism, chest CT for lung cancer screening, or diagnostic chest CT; carotid plaque noted on carotid ultrasound or angiography; or abnormal ankle-brachial index or plaque noted on peripheral arterial angiography. For clarity, calcium scoring alone is not indicative of ASCVD.

**Statin Intolerance**

Statins have been associated with muscle-related adverse effects such as myalgia (e.g., muscle aches, soreness, stiffness, or tenderness), myopathy (muscle weakness), and/or myositis (muscle inflammation). Although the incidence is variable, muscle adverse effects are reported in around 5% of patients receiving statins, but may be due to other causes (e.g., excessive exercise, other medical conditions [hypothyroidism], non-statin medications). It is advisable to assess for drug interactions as well as to check vitamin D levels and thyroid function status. Rhabdomyolysis, which is uncommon with statin therapy, is a severe muscle-related adverse effect that results in muscle breakdown associated with muscle-related symptoms (e.g., muscle pain, weakness, tenderness) along with acute renal failure and elevated creatine kinase [CK] levels (myonecrosis). In patients with statin-related muscle adverse events, symptoms may not re-occur if the patient switches to a different statin therapy. Pravastatin and fluvastatin appear to have much less intrinsic muscle toxicity than other statins and could be considered for those who had statin related intolerable muscle symptoms.

In 2014, the NLA Statin Intolerance Panel published an update. It was stated that most statin intolerance is due to myalgia. The strongest evidence at present for statin intolerance in a population is that myalgia appears but then remits with withdrawal but reoccurs with re-challenge. The incidence of statin intolerance is widely variable. The Panel states that statins are among the safest medications available. The Panel does advise that due to statin benefits, it is safe to recommend a patient continue statin therapy even when some degree of statin intolerance is present, if the patient can reasonably tolerate the statin. A pivotal trial with Praluent called ODYSSEY ALTERNATIVE defined statin intolerance as the inability to take at least two different statins due to muscle-related adverse effects, of which one statin was administered at the lowest approved starting dose. Data also suggest that many patients who are re-challenged with statin therapy after an adverse event may be able to tolerate statin therapy long-term. Of note, in the ODYSSEY ALTERNATIVE trial with Praluent, 69.8% of patients who were considered statin intolerant were treated with atorvastatin 20 mg daily and completed the double-blind 24-week portion of the trial. This suggests that re-challenge with a statin in those purported to be statin intolerant is reasonable and may lead to successful use of a statin therapy.

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Leqvio was initially FDA approved as a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA indicated as an adjunct to diet and maximally

tolerated statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia, to reduce low density lipoprotein cholesterol (LDL-C). The FDA label was later updated to indicate Leqvio as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, adults and pediatric patients aged 12 years and older with heterozygous familial hypercholesterolemia (HeFH), and pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Leqvio was investigated in three randomized, double-blind, placebo-controlled trials that enrolled 3,660 adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who were taking maximally tolerated statin therapy and who required additional LDL-C (low density lipoprotein cholesterol) lowering. Demographics and baseline disease characteristics were balanced between the treatment arms in all trials.

**LDL-C Reduction in Patients with ASCVD**

Study 1 (ORION-10) was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 1,561 patients with ASCVD were randomized 1:1 to receive subcutaneous injections of either Leqvio 284 mg or placebo on Day 1, Day 90, Day 270, and at Day 450. Patients were taking a maximally tolerated dose of statin with or without other lipid modifying therapy, and required additional LDL-C reduction. Patients were stratified by current use of statins or other lipid-modifying therapies. Patients taking PCSK9 inhibitors were excluded from the trial. The mean baseline LDL-C was 105 mg/dL. At the time of randomization, 89% of patients were receiving statin therapy and 69% were receiving high-intensity statin therapy. The primary efficacy outcome measure in Study 1 was the percent change from baseline to Day 510 in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -52% (95% CI: -56%, -49%; $p < 0.0001$).

Study 2 (ORION-11) was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 1,617 adults with ASCVD or increased risk for ASCVD were randomized 1:1 to receive subcutaneous injections of either Leqvio 284 mg or placebo on Day 1, Day 90, Day 270, and Day 450. Patients were taking a maximally tolerated dose of statin with or without other lipid modifying therapy, and required additional LDL-C reduction. Patients were stratified by country and by current use of statins or other lipid-modifying therapies. Patients taking PCSK9 inhibitors were excluded from the trial. The mean baseline LDL-C was 105 mg/dL. At the time of randomization, 95% of patients were receiving statin therapy and 78% were receiving high-intensity statin therapy. The primary efficacy outcome measure in Study 2 was the percent change from baseline to Day 510

in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was 50% (95% CI: -53%, -47%; $p < 0.0001$).

**LDL-C Reduction in Patients with HeFH**

Study 3 (ORION-9) was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 482 patients with HeFH were randomized 1:1 to receive subcutaneous injections of either Leqvio 284 mg (n = 242) or placebo (n = 240) on Day 1, Day 90, Day 270, and at Day 450. Patients with HeFH were taking a maximally tolerated dose of statin with or without other lipid modifying therapy, and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria using either the Simon Broome or WHO/Dutch Lipid Network criteria. Patients were stratified by country and by current use of statins or other lipid-modifying therapies. Patients taking PCSK9 inhibitors were excluded from the trial. The mean baseline LDL-C was 153 mg/dL. At the time of randomization, 90% of patients were receiving statin therapy and 74% were receiving high-intensity statin therapy. Fifty-two percent (52%) of patients were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin. The primary efficacy outcome measure in Study 3 was the percent change from baseline to Day 510 in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -48% (95% CI: -54%, -42%; $p < 0.0001$).

Study 4 (ORION-16) was a 12-month, randomized, double-blind, placebo-controlled trial that evaluated Leqvio in 141 pediatric patients aged 12 years and older with HeFH and elevated LDL-C. Patients were receiving maximally tolerated statin therapy with or without additional LDL-C lowering therapies, and the diagnosis of HeFH was made by genetic testing or clinical criteria. Patients were randomized 2:1 to receive subcutaneous injections of either Leqvio 284 mg (n=93) or placebo (n=48) on Day 1, Day 90, and Day 270. The mean age at baseline was 15 years, and the mean baseline LDL-C was 183 mg/dL; 93% of patients were taking statins and 23% were receiving ezetimibe. The primary efficacy outcome was the percent change from baseline to Day 330 in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 330 was -29% (96% CI: -36%, -21%; $p <0.0001$).

# References

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# Policy History

Original Effective Date: 01/01/2027
Current Effective Date: 01/01/2027
10/20/2026 UM Committee review and approval. New policy.
Next Scheduled Review Date: 10/2027

# Coding

*The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned*

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | No codes |
| HCPCS | J1306 |
| ICD-10 Diagnosis | All Related Diagnoses |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the Health Plan's Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

**NOTICE:** All codes listed on the Medical Policy require prior authorization. This ensures appropriate utilization and alignment with current clinical guidelines.

**NOTICE:** If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Blue Advantage), Blue Advantage may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Blue Advantage health plan.

**Medicare Advantage Members**
Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.