WellMed Doctors helping patients for more than 25 years	**Effective Date: 01/02/2024**	**Revision Date(s):** 12/19/23
Department: PHARMACY	**MMC Review/ Approval Date(s):** 12/27/23	**Page(s): 17**

Policy Number: 051.001

Title: Coverage Determination Policy for Lipid Modifying Agents- Leqvio (Inclisiran)

Regions: ☒ Texas ☒ New Mexico

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

WellMed Coverage Determination Policies are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support WellMed coverage decision making. WellMed may modify these Policy Guidelines at any time. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the WellMed Coverage Determination Policies is believed to be accurate and current as of the date of publication, and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

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Coverage Policy Number: 051.001

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Table of Contents **Page**

Coverage Determination:

Step Therapy Criteria

This policy supplements Medicare NCDs, LCDs, and manuals for the purpose of determining coverage under Medicare Part B medical benefits. This policy implements a prior authorization requirement for prescriptions or administrations of medical benefit injectables only. A member cannot be required under this policy to change a current drug/product. For the purposes of this policy, a current drug/product means the member has a paid claim for the drug/product within the past 365 days. For example, a new plan member currently using a particular drug/product will not be required to switch to the preferred drug/ product upon enrollment. Similarly, an existing member currently using a particular drug/product will not be required to change drugs/products in the event this policy is updated.

Step Therapy is applicable to members who have MAPD plans only

Lipid Modifying Agents:

Preferred Drug(s)/Product(s): Praluent, Repatha
Non-Preferred Drug(s)/Product(s): Leqvio

Leqvio Non-Preferred Product Step Therapy Criteria

Leqvio may be covered for the treatment of **Primary Hyperlipidemia, including Heterozygous Familial Hypercholesterolemia (HeFH) or Clinical Atherosclerotic Cardiovascular disease (ASCVD)** when **ANY** of the criteria listed below are met:

A. Trial of at least 12 consecutive weeks of either Praluent or Repatha, resulting in minimal clinical response to therapy; or

B. History of contraindication, intolerance, or adverse event(s) to Praluent or Repatha; or

C. Continuation of prior therapy within the past 365 days.

Initial/New Requests

Leqvio (Inclisiran) is proven and medically necessary for the treatment of **Primary Hyperlipidemia, including Heterozygous Familial Hypercholesterolemia (HeFH) or Clinical Atherosclerotic Cardiovascular Disease (ASCVD)** when **ALL** of the following criteria are met:

1. **Diagnosis of ONE of the following:**

   A. **Heterozygous familial hypercholesterolemia (HeFH) as confirmed by EITHER:**
      I. Pre-treatment LDL-C greater than or equal to 190 mg/dL (greater than or equal to 155 mg/dL if less than 16 years of age); and

      II. ONE of the following:
         a. Family history of myocardial infarction in first-degree relative < 60 years of age; or
         b. Family history of myocardial infarction in second-degree relative < 50 years of age; or
         c. Family history of LDL-C greater than or equal to 190 mg/dL in first- or second-degree relative; or
         d. Family history of heterozygous or homozygous familial hypercholesterolemia in first- or second-degree relative; or
         e. Family history of tendinous xanthomata and/or arcus cornealis in first- or second degree relative

OR

      I. Pre-treatment LDL-C greater than or equal to 190 mg/dL (greater than or equal to 155 mg/dL if less than 16 years of age); and

      II. ONE of the following:
         a. Functional mutation in the low density lipoprotein receptor gene (LDLR), Apolipoprotein B-100 gene (ApoB), or the proprotein convertase subtilisin/kexin type 9 gene (PCSK9); or
         b. Tendinous xanthomata; or
         c. Arcus cornealis before age 45

B. Diagnosis of Clinical Atherosclerotic cardiovascular disease (ASCVD) as confirmed by ONE of the following:

I. Acute coronary syndromes; or
II. History of myocardial infarction; or
III. Stable or unstable angina; or
IV. Coronary or other arterial revascularization; or
V. Stroke; or
VI. Transient ischemic attack; or
VII. Peripheral arterial disease presumed to be of atherosclerotic origin

C. Diagnosis of Primary hyperlipidemia with pre-treatment LDL-C greater than or equal to 190 mg/dL

2. Documentation of ONE of the following:

A. Patient has been receiving at least 12 consecutive weeks of high intensity statin therapy [i.e. atorvastatin 40-80 mg, rosuvastatin 20-40 mg] and will continue to receive a high intensity statin at maximally tolerated dose

OR

B. BOTH of the following:

I. Patient is unable to tolerate high-intensity statin as evidenced by one of the following intolerable and persistent symptoms (i.e. for more than 2 weeks) either:
   a. Myalgia (muscle symptoms without CK elevations); or
   b. Myositis (muscle symptoms with CK elevations < 10 times upper limit of normal [ULN])

AND

II. Patient has been receiving at least 12 consecutive weeks of low-intensity or moderate-intensity statin therapy [i.e. atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin ≥ 10 mg, pravastatin ≥ 10 mg, lovastatin 20-40 mg, Lescol XL (fluvastatin XL) 80 mg, fluvastatin 20-40 mg up to 40mg twice daily or Livalo (pitavastatin) ≥ 1 mg] and will continue to receive a low-intensity or moderate-intensity statin at maximally tolerated dose

OR

C. Patient is unable to tolerate low or moderate-, and high-intensity statins as evidenced by one of the following:

I. Intolerable and persistent (i.e. more than 2 weeks) symptoms for low or moderate-, and high-intensity statins as evidenced by:
   a. Myalgia (muscle symptoms without CK elevations); or
   b. Myositis (muscle symptoms with CK elevations < 10 times upper limit of normal [ULN])

II. Patient has a labeled contraindication to all statins

III. Patient has experienced rhabdomyolysis or muscle symptoms with statin treatment with CK elevations > 10 times ULN

3. **Patient has ONE of the following:**

   A. Patient has one of the following LDL-C values while on maximally tolerated lipid lowering therapy for a minimum of at least 12 weeks within the last 120 days or 120 days prior to starting Leqvio therapy:
      I. LDL-C ≥ 100 mg/dL with ASCVD; or
      II. LDL-C ≥ 130 mg/dL without ASCVD

OR

   B. BOTH of the following:

      I. Patient has one of the following LDL-C values while on maximally tolerated lipid lowering therapy for a minimum of at least 12 weeks within the last 120 days or 120 days prior to starting Leqvio therapy:

         a. LDL-C between 55 mg/dL and 99 mg/dL with ASCVD; or
         b. LDL-C between 100 mg/dL and 129 mg/dL without ASCVD

      II. And ONE of the following:
         a. Patient has been receiving at least 12 consecutive weeks of ezetimibe (Zetia) therapy as adjunct to maximally tolerated statin therapy; or
         b. Patient has a history of contraindication, or intolerance to ezetimibe

4. **Patient has received comprehensive counseling regarding appropriate diet**
5. **Leqvio will not be used in combination with PCSK9 inhibitor therapy**
6. **Leqvio dosing is in accordance with the United States Food and Drug Administration approved labeling; and**
7. **Initial authorization will be for no more than 12 months**

Renewal/Continuation of Therapy Requests

Continuation of therapy requests for Leqvio (Inclisiran) for approved indications will be approved if **ALL** of the following criteria are met:

A. Documentation of a positive clinical response to therapy from pre-treatment baseline (e.g., achieved LDL-C goal of < 100 mg/dL or achieved a 50% reduction in LDL-C levels)

B. Patient continues to receive statin at maximally tolerated dose (unless patient has an inability to take statins) in combination with Leqvio

C. Patient continues to receive comprehensive counseling regarding appropriate diet

D. Leqvio will not be used in combination with PCSK9 inhibitor therapy

E. Leqvio dosing is in accordance with the United States Food and Drug Administration approved labeling

F. Reauthorization will be for no more than 12 months

FDA Approved Dose and Indication

FDA Approved Indications	FDA Approved Dose
Treatment of adults with primary hyperlipidemia, including Heterozygous familial hypercholesterolemia (HeFH) -as an adjunct to diet and statin therapy to reduce LDL-C	• 284 mg **subQ** at initiation, 3 months after initiation, then every 6 months

NOTE:

- LEQVIO should be administered by a healthcare professional

General Background

Altherosclerosis is an accumulation of lipids (mostly low-density lipoprotein cholesterol [LDL-C]) in the inner lining of the arteries over time. An atherosclerotic cardiovascular event (such as heart attack or stroke) can be caused by an unexpected rupture of the atherosclerotic plaque. Proprotein convertase subtilisin/kexin type 9 (PCSK9), which is synthesized primarily in hepatocytes, enters circulation, and binds to hepatic LDL receptors, targeting the LDL receptors for degradation. In turn, this process reduces the capacity of the liver to bind and remove LDL-C, resulting in increased LDL-C levels. The binding of PCSK9 by monoclonal antibodies has been shown to reduce LDL-C levels by more than 50%.

Inclisiran is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).

Mechanism of Action:
Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine to facilitate uptake by hepatocytes. Utilizing the RNA interference mechanism, inclisiran directs catalytic breakdown of mRNA in hepatocytes for PCSK9. This increases LDL-C receptor recycling and expression, therefore increasing LDL-C uptake and reducing LDL-C levels in circulation.

Clinical Evidence

Heterozygous familial hypercholesterolemia (HeFH)

ORION-9 (NCT03397121) was a phase 3, randomized, double-blind, placebo-controlled trial, that evaluated the use of inclisiran in adult patients with heterozygous familial hypercholesterolemia (HeFH) who have been treated with a maximally tolerated dose of statin therapy. The study randomly assigned in a 1:1 ratio, 242 patients to receive inclisiran and 240 to receive placebo. 25% of patients had preexisting coronary artery disease and 10% had diabetes. The mean baseline LDL-C level was 153.1 mg/dL (±54 mg/dL). 90% of patients were receiving statins, including 75% who were on a high intensity statin. More than 50% were also receiving ezetimibe. The primary end points were the percent change from baseline in the LDL-C level at day 510 and time adjusted percent change from baseline in the LDL-C level between day 90 and day 540. 91.7% of patients in the inclisiran group completed the trial activities through day 540. Secondary endpoints included mean absolute change from baseline in LDL-C at day 510, time-adjusted absolute reduction from baseline between day 90 and day 540, and changes in levels of PCSK9, total cholesterol, apolipoprotein B, and non-high-density lipoprotein (HDL) cholesterol. Prespecified exploratory end points included the proportion of patients who met lipid targets for their level of cardiovascular risk and treatment response according to genotype of familial hypercholesterolemia. Study results showed at day 510, the percent change in LDL-C level was a reduction of 39.7% (95% CI -43.7 to -35.7) in the inclisiran group and an increase of 8.2% (95% CI, 4.3 to 12.2) in the placebo group; the between-group difference was -47.9 percentage points (95% CI, −53.5 to −42.3; $p < 0.001$). The time averaged percent change in the LDL cholesterol level between day 90 and day 540 was a reduction of 38.1% (95% CI, −41.1 to −35.1) in the inclisiran group and an increase of 6.2% (95% CI, 3.3 to 9.2) in the placebo group, for a between-group difference of −44.3 percentage points (95% CI, −48.5 to −40.1; $p < 0.001$). Secondary endpoint analysis showed the mean absolute change from baseline in the LDL-C level at day 510 had a between-group difference of −68.9 mg/dL(95% CI, −77.1 to −60.7; $p < 0.001$). Additionally, the time-averaged observed difference in LDL cholesterol levels between day 90 and day 540 showed a between-group difference of −62.6 mg/dL ($p < 0.001$). At day 510, a reduction from baseline in the mean LDL cholesterol level of 50% or more was reported in 38% of patients in the inclisiran group (compared to 0.8% in the placebo group; $p < 0.001$). 65.3% of patients achieved an LDL-C level of less than 100 mg/dL. The authors concluded that among adults with HeFH, those who received inclisiran had significantly lower levels of LDL-C, than those who received placebo.

Clinical Atherosclerotic Cardiovascular Disease

Two randomized, double-blind, placebo-controlled, parallel-group phase 3 trials, ORION-10 (NCT03399370) (n = 1561) and ORION-11 (NCT03400800) (n = 1617), were conducted to assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 19 months in patients at high risk for cardiovascular disease in whom LDL-C levels remained elevated, despite use of a maximally tolerated statin therapy with or without additional lipid-lowering therapy. Randomization was strategized according to background use of statins, where patients were assigned 1:1 to receive either inclisiran or placebo on days 1, 90, 270, and 450. The primary endpoints in each trial were placebo-corrected percent change in LDL-C level from baseline to day 510 and time-adjusted percent change in LDL-C level from baseline after day 90 and up to day 540. Secondary endpoints included mean absolute change from baseline in LDL-C at day 510, time-adjusted absolute reduction from baseline between day 90 and day 540, and changes in levels of PCSK9, total cholesterol, apolipoprotein B, and non-high-density lipoprotein (HDL) cholesterol. The mean LDL-C level at baseline was 104.7 ±38.3 mg/dL (ORION-10) and 105.5 ±39.1 mg/dL (ORION-11). Additionally 68% of patients were receiving high-intensity statins. The primary endpoint analysis showed at day 510, inclisiran reduced LDL-C by 52.3% (95% CI, 48.8 to 55.7) in the ORION-10 trial and by 49.9% (95% CI, 46.6 to 53.1) in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% (95% CI, 51.3 to 56.2) and 49.2% (95% CI, 46.8 to 51.6) ($p < 0.001$ for all comparisons vs. placebo). Authors concluded that reductions in LDL-C levels of approximately 50% were obtained with inclisiran, when administered every 6 months.

Definitions from the 2018 AHA/ACC Task Force clinical practice guidelines for the management of blood cholesterol: Executive Summary

High Risk Conditions defined as:
Age ≥ 65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention (PCI) outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

Major ASCVD Events defined as:
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke Symptomatic peripheral arterial disease (history of claudication with ankle brachial index < 0.85, or previous revascularization or amputation)

Very High-Risk of Future ASCVD Events: defined as a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Professional Societies

The American College of Cardiology/American Heart Association Task Force published their clinical practice guidelines for the management of blood cholesterol in 2018. In regards to those with severe hypercholesterolemia (LDL-C ≥ 190 mg/dL), the guideline recommends:

- In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥ 4.9 mmol/L) maximally tolerated statin therapy is recommended (Level I; B-R)
- In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥ 4.9 mmol/L) who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher (≥ 2.6 mmol/L) ezetimibe therapy is reasonable (Level IIa; B-R)
- In patients 20 to 75 years of age with a baseline LDL-C level 190 mg/dL or higher (≥ 4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides 300 mg/dL or lower (≤ 3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered (Level IIb; B-R)
- In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher (≥ 2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (Level IIb; BR)
- In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher (≥ 5.7 mmol/L) and who achieve an ontreatment LDL-C level of 130 mg/dL or higher (≥ 3.4 mmol/L) while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (Level IIb; C-LD)

HCPCS Code

HCPCS Code	J1306: Injection, inclisiran, 1 mg
Available Dosage Form	284 mg/1.5 mL (189 mg/mL) in a single dose PFS
Route of Administration	Subcutaneous

Acronyms

ACS = Acute coronary syndrome

ApoB = Apolipoprotein B

ASCVD = Atherosclerotic cardiovascular disease

eGFR = Estimated glomerular filtration rate

HeFH = Heterozygous familial hypercholesterolemia

CK = Creatine kinase

LDLR = Low density lipoprotein receptor gene

LDL-C = Low-density lipoprotein cholesterol

HDL-C = High-density lipoprotein cholesterol

PCSK9 = Proprotein convertase subtilisin/kexin type 9

siRNA = Small interfering ribonucleic acid

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