Leqvio® (Inclisiran)

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Instructions for Use

Table of Contents **Page**

Community Plan Policy

- Leqvio® (Inclisiran)

Coverage Rationale

See Benefit Considerations

Leqvio (inclisiran) is proven and medically necessary for the treatment of primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), or clinical atherosclerotic cardiovascular disease (ASCVD) in patients who meet all of the following criteria:[1,2]

- For **initial therapy**, **all** of the following:
  - Diagnosis of **one** of the following:
    - Heterozygous familial hypercholesterolemia (HeFH) as confirmed by **one** of the following:
      - **Both** of the following:
        - **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**
        - **One** of the following:
          - Family history of myocardial infarction in first-degree relative < 60 years of age; **or**
          - Family history of myocardial infarction in second-degree relative < 50 years of age; **or**
          - Family history of LDL-C greater than or equal to 190 mg/dL in first- or second-degree relative; **or**
          - Family history of heterozygous or homozygous familial hypercholesterolemia in first- **or** second-degree relative; **or**
          - Family history of tendinous xanthomata and/or arcus cornealis in first- or second degree relative

      or
      - **Both** of the following:
        - **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**
        - **One** of the following:
          - Functional mutation in LDL, apoB, or PCSK9 gene; **or**
          - Tendinous xanthomata; **or**
          - Arcus cornealis before age 45

or

- Atherosclerotic cardiovascular disease (ASCVD) as confirmed by **one** of the following:
  - Acute coronary syndromes; **or**
  - History of myocardial infarction; **or**
  - Stable or unstable angina; **or**
  - Coronary or other arterial revascularization; **or**
  - Stroke; **or**
  - Transient ischemic attack; **or**
  - Peripheral arterial disease presumed to be of atherosclerotic origin

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

and

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

      and
    - 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, fluvastatin XL 80 mg, fluvastatin 20-40 mg up to 40mg twice daily or pitavastatin ≥ 1 mg] and will continue to receive a low-intensity or moderate-intensity statin at maximally tolerated dose

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

      or
    - Patient has a labeled contraindication to all statins

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

and

- **One** of the following:
  - **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:
    - LDL-C ≥ 100 mg/dL with ASCVD; **or**
    - LDL-C ≥ 130 mg/dL without ASCVD

    or
  - **Both** of the following:
    - **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:
      - LDL-C between 55 mg/dL and 99 mg/dL with ASCVD; **or**
      - LDL-C between 100 mg/dL and 129 mg/dL without ASCVD

      and
    - **One** of the following:
      - Patient has been receiving at least 12 consecutive weeks of ezetimibe (Zetia®) therapy as adjunct to maximally tolerated statin therapy; **or**
      - Patient has a history of contraindication, or intolerance to ezetimibe

and
  - Patient has received comprehensive counseling regarding appropriate diet; **and**
  - Leqvio will not be used in combination with PCSK9 inhibitor therapy; **and**
  - Leqvio dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Documentation of a positive clinical response to Leqvio therapy; **and**
  - Leqvio will not be used in combination with PCSK9 inhibitor therapy; **and**
  - Leqvio dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Definitions

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 m^2)
- 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: For the purposes of this policy, Major ASCVD Events are 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: Defined as a history of multiple Major ASCVD Events or 1 major ASCVD event and multiple high-risk conditions.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1306	Injection, inclisiran, 1 mg

Diagnosis Code	Description
E75.5	Other lipid storage disorders
E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia
E78.2	Mixed hyperlipidemia
E78.49	Other hyperlipidemia

Diagnosis Code	Description
E78.5	Hyperlipidemia, unspecified
E78.9	Disorder of lipoprotein metabolism, unspecified

Background

Atherosclerosis 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%.[3,4,5,6]

Inclisiran is a cholesterol-lowering double-stranded small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc), 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.[1]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

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.[6]

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.

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:[5]

- 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; B-R)
- 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 on-treatment 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)

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Leqvio 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).[1]

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for Leqvio® (Inclisiran). Local Coverage Determinations/Articles (LCDs)/LCAs) do not exist.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed November 22, 2023)

*Preferred therapy criteria for Medicare Advantage members, refer to Medicare Part B Step Therapy Programs.

References

1. Leqvio [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; July 2023.
2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
3. Banerjee Y, Shah K, Al-Rasadi K. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med. 2012;366(25):2425-2426.
4. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. N Engl J Med. 2017;376(15):1430-1440.
5. Ray KK, Wright RS, Kallend D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med. 2020;382(16):1507-1519.
6. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. N Engl J Med. 2020;382(16):1520-1530.
7. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. American journal of epidemiology. 2004;160:407-420.
8. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Current opinion in lipidology. 2012;23:282-289.
9. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. European heart journal. 2013;34:3478-3490a.
10. Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006.

Policy History/Revision Information

Date	Summary of Changes

04/01/2024	**Coverage Rationale**
	• Replaced reference to "*Livalo* (pitavastatin)" with "pitavastatin"
	• Revised coverage criteria for **continuation of therapy**:
	  ○ Removed criterion requiring:
	  ▪ Patient continues to receive statin at maximally tolerated dose (unless patient has an inability to take statins) in combination with Leqvio
	  ▪ Patient continues to receive comprehensive counseling regarding appropriate diet
	  ○ Replaced criterion requiring "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)*" with "documentation of a positive clinical response to *Leqvio* therapy"
	Applicable Codes
	• Added ICD-10 diagnosis codes E75.5, E78.00, E78.2, E78.49, E78.5, and E78.9
	• Removed ICD-10 diagnosis code I25.10
	Supporting Information
	• Archived previous policy version 2023D00101E

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.