

Leqvio® (Inclisiran)

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[Instructions for Use](#)

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Commercial Policy
• Leqvio® (Inclisiran)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Leqvio® (Inclisiran) (for Indiana Only)
Kansas	Refer to the state’s Medicaid clinical policy
Louisiana	None
North Carolina	None

Coverage Rationale

Leqvio (inclisiran) is proven and medically necessary for the treatment of 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
 - 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
 - Coronary or other arterial revascularization; or
 - Stroke; or
 - Transient ischemic attack; or
 - Peripheral arterial disease presumed to be of atherosclerotic origin

and

- Prescribed by, a lipid specialist (e.g., cardiologist, endocrinologist, lipid specialist/lipidologist); and
- One of the following:
 - Despite adherence to PCSK9 therapy (defined by at least 12 consecutive weeks of use), one of the following:
 - Both of the following:
 - Patient has clinical ASCVD; and
 - Patient failed to achieve LDL-C goal of < 70 mg/dL
 - or
 - Both of the following:
 - Patient has severe primary hypercholesterolemia (HeFH) (pre-treatment LDL-C ≥ 190 mg/dL); and
 - Patient failed to achieve LDL-C goal of < 100 mg/dL

or

- Patient has a history of intolerance or contraindication to PCSK9 therapy
- and

- Patient will continue other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., maximally tolerated statins, ezetimibe) in combination with Leqvio; 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 therapy from pre-treatment baseline (e.g., achieved LDL-C goal of < 100 mg/dL or achieved a 50% reduction in LDL-C levels); and
 - Patient continues treatment with other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., statin, ezetimibe) in combination with Leqvio; and
 - Leqvio will not be used in combination with PCSK9 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.

*Results of prior genetic testing can be submitted as confirmation of diagnosis of HeFH, however please note that UnitedHealthcare does not currently cover genetic testing for evidence of an LDL-receptor mutation, familial defective apo B-100 or a PCSK9 mutation.

Definitions

High Risk Conditions: Defined as:

- Age ≥ 65 years
- Heterozygous familial hypercholesterolemia
- History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
- Diabetes Mellitus
- Hypertension
- Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)

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- Current smoking
- Persistently elevated LDL-C [LDL-C \geq 100 mg/dL (\geq 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
E78.01	Familial hypercholesterolemia
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris

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%.³⁻⁶

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

Clinical Evidence

Inclisiran is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).¹

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 (\pm 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) ($n = 1,561$) and ORION-11 (NCT03400800) ($n = 1,617$), 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 stratified 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 maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).¹

References

1. Leqvio [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; December 2021.
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.

Policy History/Revision Information

Date	Summary of Changes
08/01/2022	<p>Application <i>Mississippi</i></p> <ul style="list-style-type: none">• Updated language to indicate this Medical Benefit Drug Policy applies to the state of Mississippi <p>Supporting Information</p> <ul style="list-style-type: none">• Archived previous policy version CS2022D00101B

Instructions for Use

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

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professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.