Medical Policy Bulletin

Title:
Inclisiran (Leqvio®)
Policy #:
MA08.149a

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

MEDICALLY NECESSARY

1. **Criteria for Initial Approval**

   Inclisiran (Leqvio) is considered medically necessary and, therefore, covered for the treatment of primary hyperlipidemia in adults when *one* (A or B) of the following criteria are met:

   A. Individual meets ALL of the following:

- Individual has a history of clinical atherosclerotic cardiovascular disease (ASCVD) *(see Section A in the GUIDELINES portion of this medical policy bulletin)*; *and*
- Individual meets *one* of the following:
  -- Current LDL-C level greater than or equal to 70 mg/dL after at least three months of treatment with a high-intensity statin. If the inividual is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used; *or*
  -- Current LDL-C level greater than or equal to 70 mg/dL with a contraindication or intolerance to statins *(see SECTIONS B & C in the GUIDELINES portion of this medical policy bulletin)*; *and*
- Individual will continue to receive concomitant statin therapy if no contraindication or intolerance *(see SECTIONS B & C in the GUIDELINES portion of this medical policy bulletin)*; **OR**

B. Individual meets ALL of the following:

- Individual had an untreated (before any lipid-lowering therapy) LDL-C level greater than or equal to 190 mg/dL in the absence of a secondary cause; *and*
- Individual meets *one* of the following:

-- Current LDL-C level greater than or equal to 100 mg/dL after at least three months of treatment with a high-intensity statin. If the individual is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used; *or*
-- Current LDL-C level greater than or equal to 100 mg/dL with a contraindication or intolerance to statins *(see SECTIONS B & C in the GUIDELINES portion of this medical policy bulletin)*; *and*

- Individual will continue to receive concomitant statin therapy if no contraindication or intolerance *(see SECTIONS B & C in the GUIDELINES portion of this medical policy bulletin)*.

2. Continuation of Therapy

Continuation of inclisiran (Leqvio) therapy is considered medically necessary in individuals who have an indication and associated factor(s) & presetnation(s) listed in Section I above when ALL of the following criteria are met:

A. Individual has achieved or maintained an LDL-C reduction (e.g., LDL-C is now at goal, clinically acceptable lowering of LDL-C); *and*

B. Individual will continue to receive concomitant statin therapy if no contraindication or intolerance *(see SECTIONS B & C in the GUIDELINES portion of this medical policy bulletin)*.

EXPERIMENTAL/INVESTIGATIONAL

Inclisiran (Leqvio) is considered experimental/investigational and, therefore, not covered when the above criteria are not met and for all other indications unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, Inclisiran (Leqvio®) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

U.S. Food and Drug Administration (FDA)-Approved Indications

Initial Approval (December 22, 2021):

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).

Updated Label/Approval (July 2023):

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).

Section A - Clinical ASCVD

- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease (PAD) of presumed atherosclerotic origin (e.g., carotid artery stenosis, lower extremity PAD)
- Obstructive coronary artery disease (defined as fifty percent or greater stenosis on cardiac computed tomography angiogram or catheterization)
- Coronary Artery Calcium (CAC) Score ≥ 1000

Section B - Statin-Associated Muscle Symptoms (SAMS) and Statin Re-Challenge

- Score of 7 or higher on the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)
- Statin-associated elevation in creatine kinase (CK) level ≥ 10 times upper limit of normal (ULN)

Note: Statin re-challenge is NOT required for members who have experienced an elevation of CK level ≥10 times ULN after receiving lipid-lowering therapy (LLT) with a statin.

Section C - Contraindications to Statins

- Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase (ALT) level ≥ 3 times ULN)
- Pregnancy or planned pregnancy
- Breastfeeding

Dosage and Administration

Leqvio is supplied for injection as 284 mg of inclisiran in 1.5 mL (189 mg/mL) solution in a single-dose prefilled syringe. Leqvio should be administered by a healthcare professional.

The recommended dosage of Leqvio, in combination with maximally tolerated statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months.
If a planned dose is missed by less than 3 months, administer Leqvio and maintain dosing according to the individual's original schedule.
If a planned dose is missed by more than 3 months, the prescribing information says to restart with a new dosing schedule by administering Leqvio initially, again at 3 months, and then every 6 months.
Per the label, assess LDL-C when clinically indicated. The LDL-lowering effect of Leqvio may be measured as early as 30 days after initiation and anytime thereafter without regard to timing of the dose.

Source: Novartis, 2023

Description

INCLISIRAN (LEQVIO)

Inclisiran, available as Leqvio (Novartis Pharmaceuticals Corporation), is a double-stranded small interfering ribonucleic acid (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) messenger ribonucleic acid (mRNA). Inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases low-density lipoprotein cholesterol (LDL-C) receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation (Novartis, 2023).

Based on the mechanism of action, Leqvio may cause fetal harm when administered to pregnant individuals. Per the prescribing information, Leqvio should be discontinued when pregnancy is recognized. There is no information on the presence of inclisiran in human milk, the effects on the breastfed infant, or the effects on milk production. In clinical trials involving rats, inclisiran was present in the milk of lactating rats in all dose groups.

The safety and effectiveness of Leqvio have not been established in pediatric individuals.

The most common adverse reactions in clinical trials (3% or more) include injection site reaction, arthralgia, diarrhea, and bronchitis.

Clinical Atherosclerotic Cardiovascular Disease (ASCVD) and Heterozygous Familial Hypercholesterolemia (HeFH)

Clinical atherosclerotic cardiovascular disease (ASCVD) is a general term that includes conditions such as acute coronary syndrome, peripheral arterial disease, myocardial infarction and stroke. ASCVD is a heterogenous condition that is characterized by cholesterol plaque buildup in the arteries that leads to thickening and loss of elasticity in the arterial wall which increases the risk of morbidity and, if left untreated, mortality. Symptoms develop when growth or rupture of the plaque reduces or obstructs blood flow. Symptoms vary by the artery affected. It is estimated that 18.3 million American adults have ASCVD (FDA, 2021; Klimchak et al, 2020; Thanassoulis and Afshar, 2019).

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that that affects the body's ability to manage cholesterol, typically resulting in very high levels of low-density lipoprotein cholesterol (LDL-C). There are two types of FH, homozygous (HoFH) and heterozygous (HeFH). Homozygous is rare and occurs as a result of inheriting the FH gene from both parents; whereas, heterozygous is more common and results from inheriting the FH gene from one parent. Persons with HeFH generally have cholesterol levels two to three times higher than normal. HeFH increases the risk of cardiovascular events, such as heart attack, stroke, and coronary artery disease. HeFH can be life-threatening. HeFH occurs in approximately 1 in 250 individuals globally. In the absence of aggressive lipid lowering therapy, life span is significantly shortened. In addition, for a given level of LDL-C, the prognosis is worse for persons with FH than those without FH (FDA, 2021; McGowan et al., 2019; Rosenson and Durrington, 2020).

On December 22, 2021, the FDA approved Leqvio (inclisiran) injection as a treatment to be used along with diet and maximally tolerated statin therapy for adults with HeFH or clinical ASCVD who require additional lowering of LDL-C. Leqvio works to reduce circulating levels of LDL-C. FDA approval was based on the efficacy results of inclisiran that was studied in three randomized, double-blind, placebo-controlled trials (ORION-10, NCT03399370; ORION-11, NCT03400800; and ORION-9, NCT03397121) (FDA, 2021).

ORION-10 enrolled 1,561 adults with ASCVD. At day 510, the Leqvio group had an average LDL-C decrease of 51% whereas the placebo group had an average LDL-C increase of 1% (FDA, 2021).

ORION-11 enrolled 1,414 adults with ASCVD. At day 510, the Leqvio group had an average LDL-C decrease of 46% whereas the placebo group had an average LDL-C increase of 4% (FDA, 2021).

Study inclusion criteria for both ORION-10 and ORION-11 required participants to be adults aged 18 years or older, have a history of ASCVD, serum LDL-C greater than or equal to 70 mg/dL, and that participants were receiving a maximally tolerated dose of statins or have documented evidence of intolerance to all doses of at least 2 different statins.

Ray et al. (2020) state that inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin-kexin type 9 (PCSK9) and that previous studies suggest that it might also provide sustained reductions in LDL-C with infrequent dosing. Thus, the investigators conducted a phase 3 trial which enrolled individuals with ASCVD (ORION-10 trial) and individuals with ASCD or an ASCD risk equivalent (ORION-11 trial) who had elevated LDL-C levels despite receiving statin therapy at the maximum tolerated dose. Individuals were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The co-primary end points in each trial were the placebo-corrected percentage change in LDL-C level from baseline to day 510 and the time-adjusted percentage change in LDL-C level from baseline after day 90 and up to day 540. "A total of 1561 and 1617 individuals underwent randomization in the ORION-10 and ORION-11 trials, respectively. Mean (±SD) LDL cholesterol levels at baseline were 104.7±38.3 mg per deciliter (2.71±0.99 mmol per liter) and 105.5±39.1 mg per deciliter (2.73±1.01 mmol per liter), respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% (95% confidence interval [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). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and

4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent." The investigators concluded that reductions in LDL-C levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months; however, more injection-site adverse events occurred with inclisiran than with placebo.

ORION-9 was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 482 individuals 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. The primary efficacy outcome measure in Study 3 was the percent change from baseline to Day 510 in LDL-C (Novartis, 2021). At day 510, the Leqvio group had an average LDL-C decrease of 40% whereas the placebo group had an average LDL-C increase of 8% (FDA, 2021). Study inclusion criteria required participants to be adults aged 18 years or older; have a history of HeFH with a diagnosis of HeFH by genetic testing, and/or a documented history of untreated LDL-C of greater than 190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease that may indicate FH; serum LDL-C greater than or equal to 100 mg/dL at screening, and that participants were receiving a maximally tolerated dose of statins or have documented evidence of intolerance to all doses of at least 2 different statins.

Raal et al. (2020) state that monoclonal antibodies directed against PCSK9 have been shown to reduce LDL-C levels by more than 50% but require administration every 2 to 4 weeks. In a phase 2 trial, a twice-yearly injection of inclisiran, a small interfering RNA, was shown to inhibit hepatic synthesis of PCSK9 in adults with HeFH. Thus, the investigators conducted a phase 3, double-blind trial, that randomly assigned, in a 1:1 ratio, 482 adults who had HeFH to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. The two primary end points were the percent change from baseline in the LDL-C level on day 510 and the time-adjusted percent change from baseline in the LDL-C level between day 90 and day 540. At day 510, the percent change in the LDL-C level was a reduction of 39.7% (95% confidence interval [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, for a between-group difference of -47.9 percentage points ($p<0.001$). The time-averaged percent change in the LDL-C 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 ($p<0.001$). There were robust reductions in LDL-C levels in all genotypes of FH. Adverse events and serious adverse events were similar in the two groups. The investigators concluded that "among adults with HeFH, those who received inclisiran had significantly lower levels of LDL-C than those who received placebo, with an infrequent dosing regimen and an acceptable safety profile".

Primary Hyperlipidemia

In July 2023, the FDA approved a label update for Leqvio (Novartis Pharmaceuticals Corporation) as an adjunct treatment with diet and statins for adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C). In addition, label updates included the removal of the “Limitations of Use" statement regarding the undetermined effect on cardiovascular morbidity and mortality, along with four adverse events (urinary tract infection, diarrhea, pain in extremity, and dyspnea), following the updated data from the VictORION cardiovascular clinical trial program (Deswal, 2023; Novartis, 2023).

Per Novartis Pharmaceuticals Corporation, "VictORION is an innovative and robust clinical program for Leqvio, comprising 27 trials and enrolling more than 60,000 individuals in more than 50 countries worldwide. The program is designed to expand on the foundational evidence of LDL-C reduction with Leqvio in diverse individual populations to include implementation research, real-world evidence, and trials that establish its benefits on cardiovascular outcomes. A growing number of studies are planned to generate a vast array of data with major trials such as ORION-4 (secondary prevention), V (VictORION)-2-PREVENT (secondary prevention), V-1-PREVENT (high-risk primary prevention), V-INITIATE, V-INCEPTION, V-REAL, V-DIFFERENCE, and V-PLAQUE".

Ray et al. (2023) state that three phase 3 lipid-lowering trials including individuals at high risk of cardiovascular (CV) events have shown that inclisiran reduces circulating PCSK9 and LDL-C levels; however, it has yet to be determined if lowering LDL-C with inclisiran reduces the risk of CV events which is being evaluated in ongoing CV outcomes trials ORION-4 (NCT03705234) and VICTORION-2 Prevent (NCT05030428). To provide early insights into the potential for this therapeutic approach, the investigators pooled participant data from the phase 3 lipid-lowering trials, each with 18 months of follow-up and together comprised of 3655 individuals, to assess the relationship between inclisiran treatment or placebo on the risk of CV events. "Prespecified exploratory endpoint of major cardiovascular events (MACEs) included non-adjudicated CV death, cardiac arrest, non-fatal myocardial infarction (MI), and fatal and non-fatal stroke, evaluated as part of safety assessments using a standard Medical Dictionary for Regulatory Activities basket. Although not prespecified, total fatal and non-fatal MI, and stroke were also evaluated. Mean LDL-C at baseline was 2.88 mmol/L. At Day 90, the placebo-corrected percentage reduction in LDL-C with inclisiran was

50.6%, corresponding to an absolute reduction of 1.37 mmol/L (both p < 0.0001). Among 3655 individuals over 18 months, 303 (8.3%) experienced MACE, including 74 (2.0%) fatal and non-fatal MIs, and 28 (0.8%) fatal and non-fatal strokes. Inclisiran significantly reduced composite MACE [OR (95% CI): 0.74 (0.58–0.94)], but not fatal and non-fatal MIs [OR (95% CI): 0.80 (0.50–1.27)] or fatal and non-fatal stroke [OR (95% CI): 0.86 (0.41–1.81)]." The investigators concluded that their analysis offers early insights into the potential CV benefits of lowering LDL-C with inclisiran and suggests potential benefits for MACE reduction; however, these findings await confirmation in the larger CV outcomes trials of longer duration.

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 regard to those with severe hypercholesterolemia (LDL-C ≥ 190 mg/dL), the guideline recommends:

- In individuals 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 individuals 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 individuals 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 individuals 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 individuals 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)

SUMMARY

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%.

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.

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).

ORION-9 (NCT03397121) was a phase 3, randomized, double-blind, placebo-controlled trial, which evaluated the use of inclisiran in adult individuals 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 individuals to receive inclisiran and 240 to receive placebo. 25% of individuals had preexisting coronary artery disease and 10% had diabetes. The mean baseline LDL-C level was 153.1mg/dL (±54 mg/dL). 90% of individuals 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 individuals 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 individuals 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 individuals in the inclisiran group (compared to 0.8% in the placebo group; p < 0.001). 65.3% of individuals 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.

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 individuals 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 individuals 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 individuals 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.

On July 10th, 2023, Novartis announced that the US Food and Drug Administration (FDA) has approved a label update for Leqvio® (inclisiran) to enable earlier use in individuals with elevated LDL-C who have an increased risk of heart disease, as an adjunct to diet and statin therapy. This population includes those who have comorbidities such as hypertension and diabetes and have not yet had a first cardiovascular event.

Initially approved by the FDA in December 2021, Leqvio is a small interfering RNA (siRNA) therapy to lower LDL-C. The updated indication for primary hyperlipidemia allows for the expanded use of Leqvio as an adjunct to diet and statin therapy beyond the previously approved atherosclerotic cardiovascular disease (ASCVD) and heterozygous familial hypercholesterolemia (HeFH) populations.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E78.00 Pure hypercholesterolemia, unspecified

E78.011 Heterozygous familial hypercholesterolemia [HeFH]

E78.1 Pure hyperglyceridemia

E78.2 Mixed hyperlipidemia

E78.3 Hyperchylomicronemia

E78.41 Elevated Lipoprotein(a)

E78.49 Other hyperlipidemia

E78.5 Hyperlipidemia, unspecified

HCPCS Level II Code Number(s)
J1306 Injection, inclisiran, 1 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.149a:

12/15/2025	This version of the policy will become effective 12/15/2025. The following ICD-10 CM code has been removed from this policy: E78.01 Familial hypercholesterolemia The following ICD-10 CM code has been added to this policy: E78.011 Heterozygous familial hypercholesterolemia [HeFH]

Revisions From MA08.149:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	The following new policy has been developed to communicate the Company’s coverage criteria for Inclisiran (Leqvio®). The policy will become effective on 05/07/2024.

Version Effective Date:
12/15/2025
Version Issued Date:
12/15/2025
Version Reissued Date:
N/A