

This content has been created to supplement the MCG care guidelines. MCG Health has neither reviewed nor approved the modified material.

** Please note: Alignment's policy is to make 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, Alignment makes coverage decisions based on Alignment's or the delegator's policy. Benefits may vary based on contract, and individual member benefits must be verified. Alignment determines medical necessity if the benefit exists, and no contract exclusions are applicable. Although Alignment's policy is consistent with CMS's regulations and guidance, their payment methodology may differ from Medicare.*

AHC Inclisiran

AUTH: AHC-13 (AC)

MCG Health
Ambulatory Care
28th Edition

[Link to Codes](#)

- Clinical Indications
- Committee Approval
- Application
- Policy Revision History
- References
- Footnotes
- Codes

Clinical Indications

Inclisiran (Leqvio) injection was approved by the U.S. Food and Drug Administration (FDA) in December 2021 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). The effect of inclisiran on cardiovascular morbidity and mortality has not yet been determined. Inclisiran, as sponsor by the innovator drug company, was granted orphan drug designation by the FDA for the treatment homozygous familial hypercholesterolemia (HoFH) in January 2018. Inclisiran is a double-stranded small interfering RNA (siRNA) conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA. 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.

The efficacy of inclisiran was investigated in three randomized, double-blind, placebo-controlled trials that enrolled 3,457 adults with HeFH or clinical ASCVD, who were taking maximally tolerated statin therapy and who required additional LDL-C lowering. Patients taking PCSK9 inhibitors were excluded from the trials. Studies 1 and 2 (ORION-10 and ORION-11) looked at LDL-C reduction in patients with ASCVD, and Study 3 (ORION-9) in patients with HeFH. All three studies had the primary efficacy outcome measure of change from baseline to day 510 in LDL-C. Study 1 participants had a mean baseline LDL-C of 105 mg/dL, and the difference between Leqvio and placebo in mean percentage change from baseline was -52%. Study 2 participants had a mean baseline LDL-C of 101 mg/dL, and the difference between Leqvio and placebo in mean percentage change from baseline was -51%. Study 3 participants had a mean baseline LDL-C of 153 mg/dL, and the difference between Leqvio and placebo in mean percentage change from baseline was -48%. (1)(2)(3)(4)(5)(6)(7)(8)

- Initiation of inclisiran (Leqvio) meets the definition of medical necessity when ALL of the following criteria are met:
 - The member has a diagnosis of ANY of the following:
 - Heterozygous familial hypercholesterolemia (HeFH), AND the member has ANY of the following:
 - Genetic confirmation of one mutant allele at the LDLR, Apo-B, or PCSK9 gene
 - History of LDL-C greater than 190 mg/dL (greater than 4.9 mmol/L)
 - Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea)
 - "Definite" or "possible" familial hypercholesterolemia as defined by the Simon Broome criteria [A]
 - A Dutch Lipid Clinic Network Criteria score of greater than 5 [B]
 - A treated low-density lipoprotein cholesterol (LDL-C) level greater than or equal to 100 mg/dL after treatment with antihyperlipidemic agents but prior to Leqvio therapy
 - Clinical atherosclerotic cardiovascular disease (ASCVD), AND the member has ANY of the following:
 - Acute coronary syndrome
 - History of myocardial infarction

- Stable or unstable angina
 - History of coronary or other arterial revascularization
 - History of stroke or transient ischemic attack
 - Peripheral arterial disease, including aortic aneurysm, presumed to be of atherosclerotic origin
- Another FDA-approved indication for inclisiran subcutaneous injection
- The member cannot use a PCSK9 inhibitor, based on any of the following:
 - Member has tried and had an inadequate response to a PCSK9 inhibitor [e.g., Repatha (evolocumab), Praluent (alirocumab)]
 - Member has an intolerance or hypersensitivity to PCSK9 inhibitor therapy – the member's specific intolerance or hypersensitivity must be provided
 - Member has an FDA-labeled contraindication to ALL PCSK9 inhibitors - the member's specific contraindication must be provided
- The member is unable to achieve adequate lipid control on diet and maximum statin therapy, as indicated by ANY of the following:
 - Member has been adherent to high-intensity statin therapy (i.e., rosuvastatin greater than or equal to 20 mg daily, atorvastatin greater than or equal to 40 mg daily) for greater than or equal to 8 continuous weeks, and ANY of the following:
 - Member's LDL-C level after this treatment regimen remains greater than or equal to 70 mg/dL
 - Member has not achieved a 50% reduction in LDL-C from baseline (prior to treatment with high intensity statin therapy) after this treatment regimen
 - If the member has ASCVD, the member's non-HDL-C level after this treatment regimen remains greater than or equal to 100 mg/dL
 - Member has been determined to be statin intolerant by meeting ANY of the following criteria:
 - Member experienced statin-related rhabdomyolysis
 - Member experienced skeletal-related muscle symptoms [e.g., myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness)], and BOTH of the following:
 - The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products)
 - When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin)
 - Member experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products)
 - Member has a hypersensitivity to BOTH atorvastatin and rosuvastatin
 - Member has an FDA-labeled contraindication to BOTH atorvastatin and rosuvastatin - the member's specific contraindication must be provided
- Member will NOT be using the requested agent in combination with a PCSK9 inhibitor [e.g., Praluent (alirocumab), Repatha (evolocumab)] for the requested indication
- Prescriber is a specialist in the area of the member's diagnosis (e.g., cardiologist, endocrinologist, lipid specialist), or the prescriber has consulted with a specialist in the area of the member's diagnosis
- The requested dosage of inclisiran does not exceed 284 mg administered as a single subcutaneous injection initially (Day 0), again at 3 months, and then every 6 months; OR does not exceed the FDA-labeled dosing for the requested indication
- Continuation of inclisiran (Leqvio) meets the definition of medical necessity when ALL of the following criteria are met:
 - An authorization or reauthorization for inclisiran has been previously approved by Alignment Healthcare or another health plan in the past 2 years for the treatment of HeFH, ASCVD, or another FDA-approved indication (if another health plan, documentation of a health plan-paid claim for inclisiran within the past year must be submitted), OR the member has previously met ALL indication-specific initiation criteria
 - Member has had clinical benefit with inclisiran
 - Member is on the maximum tolerated dose of a high-intensity statin and/or has a documented intolerance or contraindication to statin therapy
 - Member will NOT be using the requested agent in combination with a PCSK9 inhibitor [e.g., Praluent (alirocumab), Repatha (evolocumab)] for the requested indication
 - The requested dosage of inclisiran does not exceed 284 mg administered as a single subcutaneous injection initially (Day 0), again at 3 months, and then every 6 months; OR does not exceed the FDA-labeled dosing for the requested indication

Committee Approval

- 01/09/2024, 02/20/2025

Application

- This policy applies to the following states: Arizona, California, Nevada, North Carolina, and Texas.
- Please refer to the CMS website for the most current applicable National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

Policy Revision History

- 05/26/2022: Creation date
- 06/06/2023, 12/08/2023: Revision
- 11/12/2024: Annual review, Applicable states updated, Florida removed

References

1. Leqvio (inclisiran injection, solution) [package insert]. Novartis Pharmaceuticals Corporation; East Hanover, NJ. December 2021. [Context Link 1]
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e596-e646. Epub 2019 Mar 17. [Context Link 1]
3. 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. J Am Coll Cardiol. 2019 Jun 25;73(24):3168-3209. Epub 2018 Nov 10. [Context Link 1]
4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 1/27/22. [Context Link 1]
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2022 [cited 2022 Jan 27]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/>. [Context Link 1]
6. Raal FJ, Kallend D, Ray KK, et al.; ORION-9 Investigators. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. N Engl J Med. 2020 Apr 16;382(16):1520-1530. [Context Link 1]
7. Ray KK, Wright RS, Kallend D, et al.; ORION-10 and ORION-11 Investigators. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med. 2020 Apr 16;382(16):1507-1519. [Context Link 1]
8. Robinson JG, Jayanna MB, Brown AS, et al. Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. A consensus statement from the National Lipid Association. Journal of Clinical Lipidology. July-August, 2019. 13(4): 525-537. [Context Link 1]
9. Identification and Management of Familial Hypercholesterolemia. Simon Broome Diagnostic criteria for index individuals and relatives. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK53810/>. [Context Link 1]

Footnotes

[A] Possible diagnosis of HeFH according to Simon Broome diagnostic criteria requires the patient has:

Total cholesterol greater than 6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/L in a child aged younger than 16 years, or greater than 7.5 mmol/L or LDL-C greater than 4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) AND at least one of the following:

- o Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative OR
- o Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or seconddegree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years (9) [A in Context Link 1]

[B] The Dutch Lipid Clinic Network criteria assign points based on cholesterol levels, family history of hyperlipidemia or cardiovascular disease, clinical presentation, and/or presence of identified genetic mutation affecting plasma LDL-C. A definitive diagnosis of HeFH can be made in patients with greater than 8 points. A probable diagnosis can be made in patients with 6 to 8 points.

<https://www.mdcalc.com/dutch-criteria-familial-hypercholesterolemia-fh> [B in Context Link 1]

Codes

HCPCS: J3490
