Effective Date: 05/01/2022
Last P&T Approval/Version: 04/27/2022
Next Review Due By: 04/2023
Policy Number: C23141-A

Leqvio (inclisiran)

PRODUCTS AFFECTED

Leqvio (inclisiran)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive

DIAGNOSIS:
Heterozygous familial hypercholesterolemia (HeFH), clinical atherosclerotic cardiovascular disease (ASCVD)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review

A. HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HeFH)
   1. Must have diagnosis of HeFH confirmed by Simon Broome criteria listed below:
      a) Total cholesterol greater than 290 mg/dL or LDL cholesterol greater than 190mg/dL
      AND
      b) ONE OF THE FOLLOWING: (i) first degree relative (parent, sibling, child) similarly affected or with premature CAD or with positive genetic testing for an LDL-C raising gene defect (LDL receptor, apoB, or PCSK9) OR (ii) Genetic evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation OR (iii) physical finding of tendon xanthomas or tendon xanthomas in first or second degree relative

AND

2. Clinical documentation of a therapeutic failure on, intolerance to, or contraindication to high-intensity statin therapy met by ONE (1) of the following:
   a) Adherent* on a maximally tolerated high-intensity statin therapy (daily dose of atorvastatin 40 to 80mg or rosuvastatin 20 to 40mg) and ezetimibe 10mg/day AND inability to achieve and maintain an LDL cholesterol level at or below goal (<100 mg/dL or <70 mg/dL based on patient risk) with a combination of medications, diet, and exercise by documentation of ONE (1) of the following:
      1. LDL-C ≥100 mg.dL for HeFH (evaluated within the last 3 months)
      2. LDL-C ≥70 mg/dL for ASCVD or ASCVD + FH (evaluated within the last 3 months
      3. Has not achieved a 50% reduction in LDL-C from baseline without meeting treatment goal while on maximally tolerated statin therapy

      *NOTE: Adherence is defined as at least 85% of the time as confirmed by claims history for at least 90 days OR attestation from the Provider

      OR
   b) Member has ANY of the following contraindication(s) to statin therapy [ONE]: Hypersensitivity to statins or any component of the product, Active liver disease or elevated CK levels (defined as
      >10 times the Upper Limit of Normal [ULN]), Unexplained persistent elevation of hepatic transaminases (greater than 3 times the ULN occurring on 2 or more occasions), Women who are pregnant or may become pregnant or breastfeeding
      NOTE: Laboratory tests showing evidence of muscle inflammation, alterations of liver function tests from baseline and/or liver damage required.
      OR
   c) If a re-trial of statins is not contraindicated, medical record documentation of TWO (2) statin re- trials with switching to an alternate statin [low- or moderate-intensity statin (e.g. simvastatin, pravastatin)], reducing statin dose, and/or every other day statins required. *EXCEPTIONS to re-trials may be considered by a Molina Medical Director and may require additional supporting documentation or discussion with the prescribing physician as deemed necessary by the Molina Medical Director

   AND
3. Member will be adherent to therapy AND continue adherence to maximally tolerated high-intensity statin therapy (unless contraindicated as documented above) AND ezetimibe 10 mg/day [as applicable to member therapy] Molina Reviewer: Verify member's medication fill history for compliance on maximally tolerated high-intensity statin therapy AND ezetimibe 10 mg/day
   AND
4. Documentation of NO dual therapy with PCSK9 inhibitors [Praluent (alirocumab), Repatha (evolocumab)]

B. HYPERLIPIDEMIA ASSOCIATED WITH CLINICAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE:
   1. a) Must have diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) as defined by ONE of the following:
      i) History of or current acute coronary syndrome
      ii) Myocardial infarction (MI)
      iii) Coronary or other arterial revascularization
      iv) Stroke or transient ischemic attack (TIA)

      OR

      b) Must have diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) as defined by ONE of the following: (i) Stable/unstable angina OR (ii) Peripheral arterial disease presumed to be atherosclerotic in origin

      AND

      c) Patient has at least ONE of the following risk factors that may be considered for the identification of higher-risk patient:
      i) Age greater than 65 years

ii) Current daily cigarette smoking
iii) Residual coronary artery disease with greater than or equal to 40 percent stenosis in great than or equal to 2 large vessels
iv) HDL-C less than 40 mg/dL for men and less than 50 mg/dL for women
v) hs-CRP greater than 2 mg/L, or metabolic

syndrome AND

2. Appropriate lifestyle modifications have been implemented, including an appropriate lipid-lowering diet that will continue during treatment, supported by documentation of counseling in chart notes: Total dietary fat less than 35 percent of total calories, weight loss in overweight patients, aerobic exercise, diet rich in fruits and vegetables
   AND
3. Documentation that other secondary causes of dyslipidemia have been excluded or maximally treated (e.g., high triglycerides)
   AND
4. Documentation of baseline and current LDL-C
   AND
5. Documentation of ONE of the following: baseline LDL-C between 70-189 mg/dL OR patient requires greater than 25 percent additional lowering of LDL-C OR patient has had a recent acute coronary syndrome (less than 4 months)
   AND
6. Clinical documentation of a therapeutic failure on, intolerance to, or contraindication to high-intensity statin therapy met by ONE (1) of the following:
   a) Adherent* on a maximally tolerated high-intensity statin therapy (daily dose of atorvastatin 40 to 80mg or rosuvastatin 20 to 40mg) and ezetimibe 10mg/day AND inability to achieve and maintain an LDL cholesterol level at or below goal (<100 mg/dL or <70 mg/dL based on patient risk) with a combination of medications, diet, and exercise by documentation of ONE (1) of the following:
      1. LDL-C ≥100 mg.dL for HeFH (evaluated within the last 3 months)
      2. LDL-C ≥70 mg/dL for ASCVD or ASCVD + FH (evaluated within the last 3 months
      3. Has not achieved a 50% reduction in LDL-C from baseline without meeting treatment goal while on maximally tolerated statin therapy

      *NOTE: Adherence is defined as at least 85% of the time as confirmed by claims history for at least 90 days OR attestation from the Provider
      OR
   b) Member has ANY of the following contraindication(s) to statin therapy [ONE]: Hypersensitivity to statins or any component of the product, Active liver disease or elevated CK levels (defined as
      >10 times the Upper Limit of Normal [ULN]), Unexplained persistent elevation of hepatic transaminases (greater than 3 times the ULN occurring on 2 or more occasions), Women who are pregnant or may become pregnant or breastfeeding
      NOTE: Laboratory tests showing evidence of muscle inflammation, alterations of liver function tests from baseline and/or liver damage required.
      OR
   c) If a re-trial of statins is not contraindicated, medical record documentation of TWO (2) statin re- trials with switching to an alternate statin [low- or moderate-intensity statin (e.g. simvastatin, pravastatin)], reducing statin dose, and/or every other day statins required. *EXCEPTIONS to re-trials may be considered by a Molina Medical Director and may require additional supporting documentation or discussion with the prescribing physician as deemed necessary by the Molina Medical Director

   AND
7. Member will be adherent to therapy AND continue adherence to maximally tolerated high-intensity statin therapy (unless contraindicated as documented above) AND ezetimibe 10 mg/day [as applicable to member therapy] Molina Reviewer: Verify member's medication fill history for compliance on maximally tolerated high-intensity statin therapy AND ezetimibe 10 mg/day

AND

8. Documentation of NO dual therapy with PCSK9 inhibitors [Praluent (alirocumab), Repatha (evolocumab)]

CONTINUATION OF THERAPY:

A. ALL INDICATIONS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation (documentation required)
   AND
2. Documentation of no intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by ONE of the following: Percentage reduction of LDL is greater than or equal to 40 percent compared to baseline level OR absolute LDL is less than 70 mg/dL
   AND
4. Will continue to be used in combination with a maximally tolerated statin or is statin intolerant demonstrated by documented statin-associated rhabdomyolysis to maximally tolerated high-intensity statin

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
None

AGE RESTRICTIONS:
18 years of age or older

QUANTITY:
284 mg as a single injection initially, again at 3 months, and then every 6 months thereafter

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Small interfering RNA (siRNA) PCSK9 Inhibitors

FDA-APPROVED USES:
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).

LIMITATIONS OF USE: The effect of LEQVIO on cardiovascular morbidity and mortality has not been determined.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
High-intensity statin therapy: Atorvastatin (Lipitor) 40-80 mg per day, Rosuvastatin (Crestor) 20-40 mg per day, Simvastatin (Zocor) 80 mg per day

Moderate-intensity statin therapy: Atorvastatin (Lipitor) 10-20 mg per day, Rosuvastatin (Crestor) 5-10 mg per day, Simvastatin (Zocor) 20-40 mg per day, Pravastatin (Pravachol) 40-80 mg per day, Lovastatin (Mevacor) 40mg a day, Fluvastatin XL (Lescol XL) 80 mg per day, Fluvastatin (Lescol) 40 mg twice a day, Pitavastatin (Livalo) 2-4 mg per day

Low-intensity statin therapy: Simvastatin (Zocor) 10 mg per day, Pravastatin (Pravachol) 10-20 mg per day, Lovastatin (Mevacor) 20 mg per day, Fluvastatin (Lescol) 20-40 mg per day, Pitavastatin (Livalo) 1 mg per day

Inclisiran is a first in class small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Inclisiran is a double-stranded small interfering ribonucleic acid (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 mRNA for PCSK9. 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. Inclisiran was studied in three randomized, double-blind, placebo-controlled trials (ORION program) in adults with HeFH or clinical ASCVD on maximally tolerated statin therapy who required additional LDL-C lowering. Patients taking PCSK9 inhibitors were excluded from the trials. The primary efficacy measure in these trials was percent change from baseline to day 510 in LDL-C. Inclisiran decreased LDL-C by 51%, 46%, and 40% in ORION-10, ORION-11, and ORION- 9, respectively. The mean change compared to placebo was statistically significant in each study during the 510 days: -52% (95% CI: -56%, -49%; $p < 0.0001$), -51% ((95% CI: -54%, -47%; $p < 0.0001$), -48% (95% CI: -
54%, -42%; $p < 0.0001$). Pharmacokinetic studies have shown the maintenance of LDL-C reduction through the duration of the dosing interval. Adverse reactions reported in at least 3% of inclisiran patients and more frequently than placebo were injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, dyspnea.

Clinical trials are being conducted to determine the effect of inclisiran on cardiovascular morbidity and mortality.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Leqvio (inclisiran) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy.

OTHER SPECIAL CONSIDERATIONS:
LEQVIO should be administered by a health care professional. Inject LEQVIO subcutaneously into the abdomen, upper arm, or thigh. Do not inject in areas of active skin disease or injury such as sunburns, skin

rashes, inflammation, or skin infections. Inspect LEQVIO visually before use. It should appear clear and colorless to pale yellow. Do not use if particulate matter or discoloration is seen.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J3490	Unclassified drugs

AVAILABLE DOSAGE FORMS:

Leqvio SOSY 284MG/1.5ML

REFERENCES

1. Leqvio® (inclisiran) injection, for subcutaneous use [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation: December 2021.
2. Raal F, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382(16):1520–1530.
3. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, Bisch JA, Richardson T, Jaros M, Wijngaard PLJ, Kastelein JJP; 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. doi: 10.1056/NEJMoa1912387. Epub 2020 Mar 18.
4. Warden BA, Duell PB. Inclisiran: A Novel Agent for Lowering Apolipoprotein B-containing Lipoproteins. J Cardiovasc Pharmacol. 2021 Aug 1;78(2):e157-e174. doi: 10.1097/FJC.0000000000001053.
5. Institute for Clinical and Economic Review (ICER). Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value; Final Report, March 2021.
6. 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 [published online November 10, 2018]. Circulation. 2018.
7. Tomlinson, B., Chow, E., Chan, P. and Lam, C., 2022. An evaluation of the pharmacokinetics of inclisiran in the treatment of atherosclerotic cardiovascular disease. Expert Opinion on Drug Metabolism & Toxicology, pp.1-9.

SUMMARY OF REVIEW/REVISIONS	DATE
New Development	Q2 2022