Original Effective Date: 05/01/2022
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Last P&T Approval/Version: 01/25/2023
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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. Documented diagnosis of heterozygous familial hypercholesterolemia (HeFH)
      AND
   2. Documentation member is taking a maximally tolerated intensity/dose of statin OR has an FDA labeled contraindication to statins OR had serious side effects and is unable to tolerate an alternative dosing schedule (i.e., every other day dosing)
      AND

3. Documentation member is taking ezetimibe 10mg daily OR has an FDA labeled contraindication or serious side effects
   AND
4. Documentation of current (prior to requested therapy) LDL-C (within the last 3 months)
   AND
5. Prescriber attests member will be adherent to therapy AND continue adherence to maximally tolerated dose/intensity statin therapy (unless contraindicated as documented above) AND ezetimibe 10 mg/day
   Molina Reviewer: Verify member's medication fill history for compliance on statin therapy AND ezetimibe
   AND
6. Documentation of NO dual therapy with PCSK9 inhibitors [Praluent (alirocumab), Repatha (evolocumab)]

B. HYPERLIPIDEMIA ASSOCIATED WITH CLINICAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE:
   1. a) Documentation of major atherosclerotic cardiovascular disease (ASCVD) event defined by ONE of the following:
      i) Recent acute coronary syndrome (ACS) (within the past 12 months)
      ii) Myocardial infarction (MI)
      iii) Ischemic stroke
      iv) Symptomatic PAD
      OR
      b) Documentation member has at least ONE of the following high risk factors for future ASCVD event:
      i) Age greater than 65 years
      ii) Current daily cigarette smoking
      iii) Heterozygous familial hypercholesterolemia
      iv) History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
      v) Diabetes
      vi) Hypertension
      vii) CKD (eGFR 15-59 ml/min/1.73m2)
      viii) Persistently elevated LDL-C (> 100 mg/dL despite maximally tolerated statin therapy and ezetimibe)
      ix) History of congestive heart failure
      AND
   2. Appropriate lifestyle modifications have been implemented, including adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight that will continue during treatment, supported by documentation of counseling in chart notes
      AND
   3. Documentation that other secondary causes of dyslipidemia have been excluded or maximally treated (e.g., high triglycerides, hypothyroidism, etc.)
      AND
   4. 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 3 months)
      AND
   5. Documentation of a therapeutic failure on, intolerance to, or contraindication to high-intensity statin therapy shown by ONE of the following:
      a) Adherent* to maximally tolerated high-intensity statin therapy (daily dose of atorvastatin 40 to 80mg or rosuvastatin 20 to 40mg) and ezetimibe 10mg/day along with lifestyle modifications (i.e., heart-healthy diet, regular exercise habits, avoidance of tobacco

products, and maintenance of a healthy weight) 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) by documentation of ONE of the following:

1. LDL-C greater than goal (≥100 mg.dL for HeFH or ≥70 mg/dL for ASCVD)
2. Has not achieved a 50% reduction in LDL-C from baseline without meeting treatment goal

*NOTE: Adherence to therapy 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) Documented therapeutic failure or intolerance to switching to a low- or moderate-intensity statin (e.g., simvastatin, pravastatin), OR alternative dosing schedule (i.e., every other day dosing)

AND

6. Prescriber attests member will be adherent to therapy AND continue adherence to maximally tolerated dose/ intensity statin therapy (unless contraindicated as documented above) AND ezetimibe 10 mg/day
Molina Reviewer: Verify member's medication fill history for compliance on statin therapy AND ezetimibe
AND
7. 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
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response to therapy as indicated by decrease in LDL-C OR achievement of individual LDL-C patient goal
AND
4. Prescriber attests requested agent will continue to be used in combination with a maximally tolerated statin and ezetimibe or member has an FDA labeled contraindication or serious side effects to statins and ezetimibe

DURATION OF APPROVAL:

Initial authorization: 12 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. Contraindications to Leqvio (inclisiran) include: No labeled contraindications.

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.

If a planned dose is missed by less than 3 months, administer LEQVIO and maintain dosing according to the patient's original schedule. If a planned dose is missed by more than 3 months, restart with a new dosing schedule - administer LEQVIO initially, again at 3 months, and then every 6 months.

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
J1306	Injection, inclisiran, 1 mg

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.
8. Lloyd-Jones, D. M., Morris, P. B., Ballantyne, C. M., Birtcher, K. K., Covington, A. M., DePalma, S. M., Wilkins, J. T. (2022). 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. Journal of the American College of Cardiology, 80(14), 1366-1418. doi:10.1016/j.jacc.2022.07.006

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION: Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Contraindications/Exclusions/Discontinuation Other Special Considerations Coding/Billing Information References	Q1 2023
New Development	Q2 2022