Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope	
Inclisiran [Leqvio®]	MP-RX-FP-53-23	☒ MMM MA	☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Inclisiran (Leqvio®)*, a small interfering RNA (siRNA) approved by the Food and Drug Administration (FDA) 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).

Background Information

This document addresses the use of Leqvio (inclisiran), a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA. Inclisiran is a double-stranded small interfering RNA (siRNA) designed for hepatocyte uptake using a GalNAc conjugate. It works via RNA interference to degrade mRNA for PCSK9, leading to increased LDL receptor recycling and expression on hepatocyte surfaces. This enhances LDL-C uptake by cells, reducing LDL-C levels in the blood. Leqvio is administered by a healthcare provider as a subcutaneous injection on day 1, day 90 and every 6 months thereafter. The effect of Leqvio on cardiovascular morbidity and mortality has not been determined.

In the clinical setting, statins are considered first-line drug therapy, in addition to healthy lifestyle interventions, in individuals requiring treatment for abnormal cholesterol. Other lipid lowering therapies should be considered second-line options for individuals needing additional cholesterol lowering or who cannot tolerate moderate to high doses of statins.

In 2018, the American Heart Association (AHA)/American College of Cardiology (ACC) released guidelines on the management of blood cholesterol. In very high-risk ASCVD, the guidance recommends considering adding non-statins to statin therapy when LDL-C remains greater than or equal to 70 mg/dL. Ezetimibe is the first agent to consider adding on to maximally tolerated statin therapy. PCSK9 inhibitors can be considered for addition if LDL-C remains greater than or equal to 70 mg/dL on statin therapy combined with ezetimibe.

The 2018 AHA/ACC guidelines recommend using an LDL-C threshold of greater than or equal to 100 mg/dL to consider adding non-statins to statin therapy in individuals with severe primary

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hypercholesterolemia. Ezetimibe is the first non-statin to consider adding to therapy. PCSK9 inhibitors can be considered for addition if LDL-C remains greater than or equal to 100 mg/dL on statin therapy combined with ezetimibe.

In 2022, the ACC released an expert consensus decision pathway on the role of non-statin therapies for LDL-C lowering. In very high-risk ASCVD, the pathway recommends considering adding non-statins to statin therapy when LDL-C remains greater than or equal to 55 mg/dL. Ezetimibe and/or PCSK9 monoclonal antibodies are the first agents to consider adding to statin therapy. Nexletol and Leqvio are secondary options that can be considered for addition. In lower risk ASCVD, the pathway recommends considering adding non-statins to statin therapy when LDLC remains greater than or equal to 70 mg/dL. The preference for agent addition generally follows the recommendations for individuals at very high risk.

The 2022 pathway recommends using an LDL-C threshold of greater than or equal to 100 mg/dL to consider adding non-statins to statin therapy in individuals without ASCVD but with baseline LDL-C greater than or equal to 190 mg/dL. Ezetimibe and/or PCSK9 monoclonal antibodies are the first agents to consider adding to statin therapy. Nexletol and Leqvio are secondary options that can be considered for addition.

Statins have labeled warnings for liver enzyme abnormalities and skeletal muscle effects including myopathy and rhabdomyolysis. Statin-induced adverse events leading to some degree of intolerance is reported in as many as 5% to 30% of individuals although incidence and prevalence vary. The National Lipid Association (NLA) has provided guidance defining statin intolerance as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin or partial intolerance, with inability to tolerate the dose necessary to achieve the individual-specific therapeutic objective. To classify an individual as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.

World Health Organization (WHO)/Dutch Lipid Clinic Network Criteria for Familial Hypercholesterolemia (FH) Diagnosis

Criteria	Points
Family History	
Known premature coronary and vascular disease (men <55 years, women <60 years) in first degree relative	1
Known LDL-C >95th percentile in first degree relative	1
Tendon xanthoma and/or corneal arcus in first degree relative	2
Children aged <18 years with LDL-C >95th percentile	2
Personal Clinical History	
Premature coronary artery disease (men <55 years, women <60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, women <60 years)	1
Clinical Exam	
Tendon xanthoma	6
Corneal arcus in individual aged <45 years	4

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LDL-C Level	
> 329 mg/dL (>8.5 mmol/L)	8
250-329 mg/dL (6.5-8.4 mmol/L)	5
190-249 mg/dL (5.0-6.4 mmol/L)	3
155-189 mg/dL (4.0-4.9 mmol/L)	1
Genetic Testing	
Functional mutation in LDLR, ApoB or PCSK9 gene	8

Scoring: Definite FH:> 8 points; Probable FH: 6-8 points; Possible FH: 3-5 points; Unlikely FH: 0-2 points

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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	Description
J1306	Injection, inclisiran, 1 mg [Leqvio]

ICD-10	Description
E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia
E78.2	Mixed hyperlipidemia
E78.41	Elevated Lipoprotein(a)
E78.49	Other hyperlipidemia
E78.5	Hyperlipidemia, unspecified
I20.0-I20.9	Angina pectoris
I21.01-I21.B	Acute myocardial infarction
I22.0-I22.9	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
I23.7	Postinfarction angina
I24.0-I24.9	Other acute ischemic heart diseases
I25.10-I25.9	Chronic ischemic heart disease
Z83.42	Family history of familial hypercholesterolemia
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits.
Z95.1	Presence of aorto coronary bypass graft
Z95.5	Presence of coronary angioplasty implant and graft
Z95.820-Z95.828	Presence of other vascular implants and grafts

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Inclisiran (Leqvio®)

A. Criteria For Initial Approval

Initial requests for Leqvio (inclisiran) may be approved when the following criteria are met:

i. Individual is at high risk for atherosclerotic cardiovascular disease (ASCVD) events as identified by one of the following:
   A. Individual has Heterozygous Familial Hypercholesterolemia (HeFH) confirmed by (Singh 2015; WHO 1999):
      1. Presence of a mutation in LDLR, ApoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene;

      OR

      2. WHO/Dutch Lipid Clinic Network criteria with score of greater than eight points;

   OR

   B. Individual has a history of clinical atherosclerotic cardiovascular disease (ASCVD) including one or more of the following (AHA/ACC 2018):
      1. Acute coronary syndrome;
      2. Coronary artery disease (CAD);
      3. History of myocardial infarction (MI);
      4. Stable or unstable angina;
      5. Coronary or other arterial revascularization;
      6. Stroke;
      7. Transient ischemic attack (TIA);
      8. Peripheral arterial disease (PAD);

   OR

   C. Individual has primary hyperlipidemia with an untreated LDL-C greater than or equal to 190 mg/dL (ACC 2022); **AND**

ii. Individual meets one of the following:
   A. Individual is on high intensity statin therapy or statin therapy at the maximum tolerated dose (high intensity statin is defined as atorvastatin 40 mg or higher or rosuvastatin 20 mg or higher) (AHA/ACC 2018);

   OR

   B. Individual is statin intolerant based on one of the following:
      1. Inability to tolerate at least two statins, with at least one started at the lowest starting daily dose, demonstrated by adverse effects associated with statin therapy that resolve or improve with dose reduction or discontinuation (NLA 2022);

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OR

2. Statin associated rhabdomyolysis or immune-mediated necrotizing myopathy (IMNM) after a trial of one statin;

OR

C. Individual has a contraindication for statin therapy including but not limited to active liver disease, unexplained persistent elevation of hepatic transaminases or pregnancy;

AND

iii. Individual has achieved suboptimal lipid lowering response despite at least 90 days of compliant lipid lowering therapy and lifestyle modifications as defined (AHA/ACC 2018, ACC 2022):

A. For individuals where initial LDL-C is known:

1. Less than 50% reduction in LDL-C;

OR

B. For individuals where initial LDL-C is unknown:

1. ASCVD and LDL-C remains greater than or equal to 55 mg/dL;

OR

2. No history of ASCVD and LDL-C remains greater than or equal to 100 mg/dL.

B. Criteria for Continuation of Therapy

Continuation requests for Leqvio (inclisiran) may be approved when the following criteria are met:

i. Individual continues to use in combination with maximally tolerated statin therapy (unless contraindication or individual is statin intolerant); **AND**

ii. Individual has achieved LDL-C reduction.

C. Conditions not Covered

Leqvio (inclisiran) may not be approved for the following:

i. In combination with Praluent or Repatha;

OR

ii. When the above criteria are not met and for all other indications.

D. Authorization Duration

i. Initial Approval Duration: 1 year

ii. Continuation Approval Duration: 1 year

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Limits or Restrictions

A. Therapeutic Alternatives

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Limit
Leqvio (inclisiran) 284 mg/1.5 mL prefilled syringe	1 syringe per 6 months
Exceptions	
Initiation of therapy: May approve one additional prefilled syringe within the first six months of initiating therapy	

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Reference Information

1. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022; Aug 24:[Epub ahead of print].
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3. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 13, 2022.
4. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
5. 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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.
6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
7. Singh S, Bittner V. Familial hypercholesterolemia--epidemiology, diagnosis, and screening. Curr Atheroscler Rep. 2015; 17(2):482.
8. World Health Organization. Familial hypercholesterolemia—report of a second WHO Consultation. Geneva, Switzerland: World Health Organization, 1999. Available at: http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf?ua=1. Accessed: July 17, 2022.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Annual Review 8/18/24	Update Background Information. Update criteria with additional primary hyperlipidemia indication. Coding Reviewed: Add ICD-10-CM E78.00, E78.01, E78.2, E78.41, E78.49, E78.5, I21.01-I21.B, I22.0-I22.9, Z83.42, Z86.73, Z95.1, Z95.5, and Z95.820-Z95.828. Expanded codes I20.8, I20.9 to I20.0-I20.9. Changed I25.2-I25.9 to I25.10-I25.9 and changed the wording for the indication to Chronic ischemic heart disease. Changed I24.0-I24.8 to I24.0-I24.9 and changed the wording for the indication to Other acute ischemic heart diseases. Update criteria by removing step through ezetimibe; update LDL-C requirement for individuals with history of ASCVD; extend initial approval duration. Wording and formatting changes.	2/24/2025	3/6/2025
Policy Inception 8/18/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023