Subject: Leqvio (inclisiran)

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Overview

This document addresses the use of Leqvio (inclisiran), a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA approved by the Food and Drug Administration 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). 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 can't 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 to consider 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 a 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 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.

Statins have labeled warnings for liver enzyme abnormalities and skeletal muscle effects including myopathy and rhabdomyolysis. Statin-induced adverse events leading to intolerance are possible, but it is estimated 74% of individuals considered statin intolerant can successfully be treated with a statin long-term (based on observational data). Definitions of statin intolerance are variable but the National Lipid Association (NLA) has provided guidance defining statin intolerance as a clinical syndrome characterized by the inability to tolerate at least two statins, one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (including hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise and underlying muscle disease).

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
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

Clinical criteria

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.

Leqvio (inclisiran)

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);

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 intolerable symptoms or clinically significant biomarker changes (NLA 2014); **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 active liver disease, unexplained persistent elevation of hepatic transaminases or pregnancy;

AND

III. Individual is on ezetimibe in addition to statin therapy (only applies to individuals on statin therapy) (AHA/ACC 2018);

AND

IV. 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):
   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 70 mg/dL; **OR**
      2. No history of ASCVD and LDL-C remains greater than or equal to 100 mg/dL.

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

I. Individual continues to receive concomitant maximally tolerated statin therapy (unless contraindication or individual is statin intolerant); **AND**

II. Confirmation of LDL-C reduction has been provided.

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.

Initial Approval Duration: 6 months
Continuation Approval Duration: 1 year

Quantity Limits

Leqvio (inclisiran) Quantity Limit

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

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J3490	Unclassified drugs (when specified as [Leqvio] (inclisiran))

ICD-10 Diagnosis

	All diagnoses pend

Document history

New: 01/04/2022
Document History:

- 01/04/2022 – Select Review: Add clinical criteria and quantity limit for Leqvio. Coding Reviewed: Added HCPCS J3490. All diagnoses pend.

References

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7. 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: December 31, 2021.

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.