

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Related Products – Leqvio Prior Authorization Policy

- Leqvio® (inclisiran subcutaneous injection – Novartis)

REVIEW DATE: 04/13/2022

OVERVIEW

Leqvio, a small interfering ribonucleic acid (RNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) messenger RNA, is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with the following:¹

- Clinical **atherosclerotic cardiovascular disease (ASCVD)** for those who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- **Heterozygous familial hypercholesterolemia (HeFH)** for those who require additional lowering of LDL-C.

The effect of Leqvio on cardiovascular (CV) morbidity and mortality have not been established.¹ The safety and effectiveness have not been established in pediatric patients.

Disease Overview

ASCVD (including CV disease) is a leading cause of morbidity and mortality worldwide.²⁻⁴ ASCVD is defined as patients who have experienced an acute coronary syndrome (ACS) event, those with a history of myocardial infarction (MI), stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease.^{3,4} Lowering LDL-C levels has been strongly correlated to reduce the risk of subsequent CV disease among patients with ASCVD.

Familial hypercholesterolemia is an autosomal dominant genetic disease that is noted by markedly elevated LDL-C, often at a young age, and premature ASCVD.⁵⁻⁸ The condition is often undiagnosed and untreated. It is estimated that 620,000 patients in the US have familial hypercholesterolemia which includes HeFH and homozygous familial hypercholesterolemia (HoFH). HeFH is the most common of the defects and occurs in approximately 1 in 200 to 1 in 500 patients. LDL-C levels in adults who are untreated usually are > 220 mg/dL. HoFH is less common (one in 1 million people) and is associated with extremely elevated LDL-C levels (400 mg/dL [untreated]). Diagnosis may be considered by genetic testing. However, because a substantial percentage of patients do not have an identifiable mutation, the condition is clinically diagnosed on the basis of a combination of physical findings, family history, early-onset ASCVD, and LDL-C levels. A LDL-C \geq 190 mg/dL in adults suggests a diagnosis of HeFH. Patients may also have physical findings such as cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma. The Simon Broome criteria and the Dutch Lipid Clinical Network Criteria are also useful for diagnosing HeFH and examine various factors such as cholesterol level, the presence of clinical findings, family history, and genetic analysis. Treatment to manage LDL-C levels is needed to prevent CV disease from developing in these patients with statins recommended as first-line. Other therapies are also added to reduce LDL-C.

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Dosing Information

Leqvio is given as a subcutaneous injection and should be administered by a healthcare professional. The dose is 284 mg given as a single subcutaneous injection initially, again at 3 months, and then once every 6 months.

Guidelines

Leqvio is not addressed in guidelines. Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.^{3-5,9-12} For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of $\geq 50\%$.

- The **American Heart Association (AHA)/American College of Cardiology guidelines on the management of blood cholesterol (2018)** define ACSVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, TIA, or peripheral arterial disease.^{2,3} An LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk.
- **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).¹² Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network Criteria and Simon Broome Criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Leqvio. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Leqvio is recommended in those who meet one of the following criteria:

FDA-Approved Indications

- 1. Atherosclerotic Cardiovascular Disease.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
 - A)** Patient is ≥ 18 years of age; AND
 - B)** Patient has had one of the following conditions or diagnoses (i, ii, iii, iv, or v):
 - i.** A previous myocardial infarction or a history of an acute coronary syndrome; OR
 - ii.** Angina (stable or unstable); OR
 - iii.** A past history of stroke or transient ischemic attack; OR
 - iv.** Peripheral arterial disease; OR
 - v.** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.
 - C)** Patient meets one of the following criteria (i or ii):
 - i.** Patient meets all of the following (a, b, and c):

- a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin \geq 40 mg daily; rosuvastatin \geq 20 mg daily [as a single entity or as a combination product]); AND
 - b) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for \geq 8 continuous weeks; AND
 - c) Low-density lipoprotein cholesterol level after this treatment regimen remains \geq 70 mg/dL; OR
 - ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
 - a) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a \geq 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
 - b) Patient meets all of the following [(1), (2), and (3)]:
 - (1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
 - (2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
 - (3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).
Note: Examples of skeletal muscle symptoms include myopathy or myalgia.
 - D) Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders.
2. **Heterozygous Familial Hypercholesterolemia (HeFH).** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- A) Patient is \geq 18 years of age; AND
 - B) Patient meets one of the following criteria (i, ii, or iii):
 - i. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level \geq 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
 - ii. Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR
 - iii. Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting one of the following diagnostic criteria thresholds (a or b):
 - a) Patient meets both of the following [(1) and (2)]:
 - (1) Prescriber used the Dutch Lipid Network criteria to diagnose heterozygous familial hypercholesterolemia; AND
 - (2) Patient had a score $>$ 5; OR
 - b) Patient meets both of the following [(1) and (2)]:
 - (1) Prescriber used the Simon Broome criteria to diagnose heterozygous familial hypercholesterolemia; AND
 - (2) Patient met the threshold for “definite” or “possible (or probable)” familial hypercholesterolemia; AND
 - C) Patient meets one of the following criteria (i or ii):
 - i. Patient meets all of the following criteria (a, b, and c):
 - a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin \geq 40 mg daily; rosuvastatin \geq 20 mg daily [as a single-entity or as a combination product]); AND

- b) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
- c) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
- ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
 - a) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [$a \geq 0.5$ mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
 - b) Patient meets all of the following [(1), (2), and (3)]:
 - (1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
 - (2) The skeletal muscle-related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
 - (3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).
Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.
- D) Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leqvio is not recommended in the following situations:

1. **Concurrent use of Leqvio with Repatha (evolocumab subcutaneous injection) or Praluent (alirocumab subcutaneous injection).** Repatha and Praluent are PCSK9 inhibitors and should not be used with Leqvio due to a similar mechanism of action.¹ Patients receiving PCSK9 inhibitors were excluded from the pivotal trials with Leqvio.
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Leqvio[®] subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis; December 2021.
2. American Heart Association. 2021 Heart Disease and Stroke Statistics Updated Fact Sheet At-a-Glance. Available at: <https://www.heart.org/-/media/phd-files-2/science-news/2/2021-heart-and-stroke-stat-update/2021-heart-disease-and-stroke-statistics-update-fact-sheet-at-a-glance.pdf?la=en> Accessed on April 9, 2022.
3. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-2934.
4. Grundy SM, Stone NJ, Bailey AL, et al. ACC/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. *Circulation.* 2019;139(25):e1082-e1143.
5. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J Clin Lipidol.* 2011;5:S1-S8.
6. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol.* 2012;23:282-289.

7. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia. A scientific statement from the American Heart Association. *Circulation*. 2015;132(22):2167-2192.
8. McGowan MP, Dehkordi SHH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc*. 2019;8:e013225.
9. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2016;68(1):92-125.
10. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease. *J Am Coll Cardiol*. 2017;70(14):1785-1822.
11. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-full report. *J Clin Lipidol*. 2015;9:129-169.
12. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia. A scientific statement from the American Heart Association. *Circulation*. 2015;132(22):2167-2192.

HISTORY

| Type of Revision | Summary of Changes | Review Date |
|-----------------------|--|-------------|
| New Policy | -- | 01/03/2022 |
| Early Annual Revision | No criteria changes. The header of the policy was changed from “Hyperlipidemia” to “Proprotein Convertase Subtilisin Kexin Type 9 Related Products.” | 04/13/2022 |

APPENDIX A

Simon Broome Register Diagnostic Criteria.⁶

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| Definite Familial Hypercholesterolemia |
| Raised cholesterol |
| --Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR |
| --Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age; |
| AND |
| --Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle); |
| OR |
| DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation. |
| Possible (or Probable) Familial Hypercholesterolemia |
| Raised cholesterol |
| --Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR |
| --Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age; |
| AND |
| Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative; |
| OR |
| Raised cholesterol |
| --Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR |
| --Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age; |
| AND |
| Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years. |

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.¹²

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.