Corporate Medical Policy: Inclisiran (Leqvio®) **"Notification"** **POLICY EFFECTIVE AUGUST 1, 2026**

Restricted Product(s):

- inclisiran (Leqvio®) subcutaneous injection for administration by a healthcare professional

FDA Approved Use:

- As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:
  - Adults with hypercholesterolemia
  - Adults and pediatric patients aged 12 years and older with heterozygous familial hypercholesterolemia (HeFH)
  - Pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH)

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient has a diagnosis of **heterozygous familial hypercholesterolemia (HeFH)**; **AND**
   a. The patient is 12 years of age or older; **AND**
   b. The diagnosis has been confirmed by ONE of the following:
      i. Genetic confirmation of one mutant allele at the *LDLR*, *Apo-B*, *PCSK9*, or *1/LDLRAP1* gene; **OR**
      ii. History of low-density lipoprotein cholesterol (LDL-C) greater than 190 mg/dL (pretreatment); **OR**
      iii. Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea); **OR**
      iv. "Definite" or "possible" familial hypercholesterolemia as defined by the Simon Broome criteria; **OR**
      v. A Dutch Lipid Clinic Network Criteria score of greater than 5; **OR**

2. The patient has a diagnosis of **hypercholesterolemia**; **AND**
   a. The patient is 18 years of age or older; **AND**
   b. ONE of the following:
      i. The patient has a diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD), defined as a history of ONE of the following:
         1. Acute coronary syndrome; **OR**
         2. Myocardial infarction; **OR**

3. Stable or unstable angina; **OR**
4. Coronary or other arterial revascularization; **OR**
5. Stroke; **OR**
6. Transient ischemic attack; **OR**
7. Peripheral arterial disease, including aortic aneurysm, presumed to be of atherosclerotic origin; **OR**

ii. The patient has a greater than or equal to 10% 10-year ASCVD risk; **OR**
iii. The patient has severe hypercholesterolemia (i.e., history of LDL-C greater than or equal to 190 mg/dL [pretreatment]); **OR**
iv. The patient has subclinical atherosclerosis (i.e., coronary artery calcium [CAC] score greater than or equal to 100 Agatston units); **OR**

3. The patient has a diagnosis of **homozygous familial hypercholesterolemia (HoFH)**; **AND**
   a. The patient is 12 to 17 years of age; **AND**
   b. The diagnosis has been confirmed by ONE of the following **[medical record documentation required]**:
      i. BOTH of the following:
         1. Genetic confirmation of two mutant alleles at the *LDLR, Apo-B, PCSK9,* or *LDLRAP1* gene; **AND**
         2. The patient does NOT have two *LDLR* negative alleles (null homozygous); **OR**
      ii. History of untreated LDL-C >400 mg/dL with ONE of the following:
         1. Clinical manifestations of HoFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma) before 10 years of age; **OR**
         2. Untreated elevated LDL-C levels consistent with heterozygous FH in both parents (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH); **AND**

4. ALL of the following:
   a. ONE of the following:
      i. The patient has previously been treated with and adherent to high-intensity or maximally tolerated dose of statin therapy for ≥8 continuous weeks; **OR**
      ii. The patient has been determined to be statin intolerant, defined as experiencing ONE of the following:
         1. Statin-related rhabdomyolysis; **OR**
         2. Statin-related skeletal muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) with the trial of at least TWO statin therapies that resolved upon discontinuation; **OR**
         3. Elevations in hepatic transaminase due to statin therapy; **OR**
      iii. The patient has an FDA labeled contraindication or hypersensitivity to ALL statin therapies; **AND**
   b. ONE of the following:
      i. The patient has a diagnosis of HoFH and ONE of the following:

1. The patient has tried and had an inadequate response despite adherence to Repatha (evolocumab) **[medical record documentation required]**; **OR**
2. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to Repatha (evolocumab) **[medical record documentation required]**; **OR**

ii. The patient has tried and had an inadequate response despite adherence to a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (e.g., Lerochol [lerodalcibep-liga], Praluent [alirocumab], Repatha [evolocumab]) **[medical record documentation required]**; **OR**

iii. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL PCSK9 inhibitors (i.e., Lerochol [lerodalcibep-liga], Praluent [alirocumab], AND Repatha [evolocumab]) **[medical record documentation required]**; **AND**

c. ONE of the following:

i. The patient is 12 to 17 years of age AND the patient's LDL-C level after this treatment regimen remains above goal (i.e., ≥100 mg/dL for HoFH; ≥130 mg/dL for HeFH) **[medical record documentation required]**; **OR**

ii. The patient is ≥18 years of age AND the patient's LDL-C level after this treatment regimen remains above goal (i.e., ≥100 mg/dL for HoFH; ≥70 mg/dL for HeFH; ≥55 mg/dL for ASCVD or major ASCVD risk factors) **[medical record documentation required]**; **AND**

5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, endocrinologist, geneticist, lipid specialist) or has consulted with a specialist in the area of the patient's diagnosis; **AND**
6. The patient will NOT be using the requested agent in combination with a PCSK9 inhibitor (e.g., Lerochol [lerodalcibep-liga], Praluent [alirocumab], Repatha [evolocumab]) for the requested indication; **AND**
7. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
8. For requests for injection or infusion administration of the requested medication in an inpatient or outpatient hospital setting, Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy; **AND**
3. The patient has had clinical benefit with the requested agent (e.g., reduction in LDL-C level from baseline prior to starting therapy with the requested agent) **[medical record documentation required]**; **AND**
4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, endocrinologist, geneticist, lipid specialist) or has consulted with a specialist in the area of the patient's diagnosis; **AND**

5. The patient will NOT be using the requested agent in combination with a PCSK9 inhibitor (e.g., Lerochol [lerodalcibep-liga], Praluent [alirocumab], Repatha [evolocumab]) for the requested indication; **AND**
6. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
7. For requests for injection or infusion administration of the requested medication in an inpatient or outpatient hospital setting, Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
inclisiran (Leqvio®) subcutaneous (SC) injection	Hypercholesterolemia in adults HeFH in patients ≥ 12 years old HoFH in patients 12 to 17 years old	SC: 284 mg as a single injection initially, then 284 mg at 3 months, then 284 mg every 6 months thereafter	J1306	Initial: 852 Continuation: 568

***Maximum units allowed for duration of approval**

***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:
    a. History of a severe adverse event following the injection or infusion of the requested medication (i.e., anaphylaxis, seizure, thromboembolism, myocardial infarction, renal failure); **OR**
    b. Conditions that cause an increased risk for severe adverse event (i.e., unstable renal function, cardiopulmonary conditions, unstable vascular access); **OR**
    c. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
    d. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
    e. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
    f. Re-initiation of therapy, defined as ONE of the following:

   i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
   ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
 g. Requirement of a change in the requested restricted product formulation; **AND**
3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

References: all information referenced is from FDA package insert unless otherwise noted below.

1. Raal FJ, Kallend D, Ray KK, et al.; ORION-9 Investigators. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020 Apr;382(16):1520-1530.
2. Ray KK, Wright RS, Kallend D, et al.; ORION-10 and ORION-11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020 Apr;382(16):1507-1519.
3. Writing Committee, Lloyd-Jones DM, Morris PB, et al. 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 [published correction appears in *J Am Coll Cardiol*. 2023 Jan;81(1):104]. *J Am Coll Cardiol*. 2022;80(14):1366-1418.
4. Patel SB, Wyne KL, Samina Afreen, et al. American Association of Clinical Endocrinology Clinical Practice Guideline on Pharmacologic Management of Adults with Dyslipidemia. *Endocrine Practice*. 2025;31(2).
5. Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients with Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2025;151(13):e771-e862.
6. Blumenthal, R, Morris, P, Gaudino, M. et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2026;153(17):e1154-e1276.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q1 annually.

August 2026: Criteria change: For HeFH: Reformatted initial diagnostic confirmation criteria for clarity and removed option of treated LDL-C ≥100 mg/dL after treatment with antihyperlipidemic agents. For hypercholesterolemia: Reformatted criteria for ASCVD, primary hyperlipidemia, and ASCVD risk sections to instead confirm the patient has a diagnosis of hypercholesterolemia and either ASCVD, ASCVD

risk, severe hypercholesterolemia, or subclinical atherosclerosis; Adjusted ASCVD risk from 20% to 10% and CAC score (subclinical atherosclerosis) from 300 to 100 to align with updated clinical guideline recommendations. For HoFH: Reformatted initial diagnostic confirmation criteria for clarity. Adjusted statin therapy trial requirement to add allowance for maximally tolerated dose of statin therapy and to remove specific product and dosing criteria, allowing for any high-intensity or maximally tolerated statin therapy. Refined the requirements for statin intolerance. Added newly approved Lerochol as an option within PCSK9 inhibitor trial requirement. Adjusted and reformatted LDL-C goals (12 to 17 years: ≥100 mg/dL for HoFH; 18 years and older: ≥100 mg/dL for HoFH, ≥70 mg/dL for HeFH, ≥55 mg/dL if ASCVD or at high risk for ASCVD) to align with updated clinical guideline recommendations and added required medical record documentation of failure to achieve target LDL-C despite treatment with other LDL-C lowering therapies. For continuation criteria, added required medical record documentation to demonstrate clinical benefit with the requested agent. Updated formatting throughout policy for clarity. **Policy notification given 6/1/2026 for effective date 8/1/2026**.

March 2026: Criteria change: Added new indication for patients 12 to 17 years of age with HoFH with corresponding criteria and dosing table updates. Updated step through PCSK-9 inhibitor to only require Repatha if the patient has a diagnosis of HoFH. Expanded indication for HeFH to include pediatric patients 12 years and older according to updated FDA labeling with corresponding criteria updates. Minor formatting changes made throughout policy for clarity.

November 2025: Criteria change: Added newly approved expanded indication for hypercholesterolemia with removal of use as an adjunct to statin therapy, according to updated FDA label. For HeFH indication, added *1/LDLRAP1* gene as an option for genetic confirmation of gene mutation, provided clarification that the requirement for history of LDL-C > 190 mg/dL is pretreatment, and provided clarification that antihyperlipidemic agents indicate statin therapy with or without ezetimibe. For primary hyperlipidemia indication, changed untreated LDL-C requirement to ≥ 190 mg/dL to align with clinical guidelines. Simplified 10-year ASCVD risk criteria to only include ASCVD risk ≥ 20% (removed additional criteria requirements and varying LDL-C goals according to category of risk in these patients) and an LDL-C level above goal while on maximally tolerated statins. Clarified trial and failure criteria for PCSK9 inhibitor therapy to include the following language: despite adherence to treatment. Consolidated definition of failure of high-intensity statin therapy and PCSK9 inhibitor therapy, and adjusted and re-categorized goals according to updated goals per clinical guidelines (LDL-C remaining ≥70 mg/dL or ≥55 mg/dL if established ASCVD or at high risk for ASCVD). Added geneticist as an additional specialist option. Within continuation criteria, added additional clarification of clinical benefit indicated by reduction in LDL-C level from baseline prior to starting therapy with the requested agent, and removed statin combination therapy requirement. Updated Site of Care medical necessity criteria to add additional bypass for patients with a history of severe adverse events or conditions that cause an increased risk for severe adverse event to align with the Place of Service for Medical Infusions policy for clarity of intent. Updated formatting throughout policy for clarity with no change to intent.

October 2023: Criteria change: Added newly approved updated indication for primary hyperlipidemia, including HeFH, to reduce low-density lipoprotein cholesterol (LDL-C), as an adjunct to diet and statin therapy. Added associated criteria for primary hyperlipidemia and ≥ 20% 10-year ASCVD risk. Added criteria for very high risk patients with LDL ≥ 55 mg/dL after high intensity statin therapy. Minor formatting changes made throughout policy for consistency and clarity.

July 2022: Coding update: Added HCPCS code J1306 to dosing reference table effective 7/1/2022, deleted C9399, J3490, and J3590 termed 6/30/2022.

March 2022: Criteria change: Updated trial and failure PCSK-9 agents to include any PCSK-9 inhibitor.
February 2022: Original medical policy criteria issued.