Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR042.0625	**CARDIOVASCULAR AGENTS** **PCSK9 INHIBITORS** **Leqvio®** (inclisiran sodium syringe)
Effective Date: 8/1/2025	**Review/Revised Date**: 06/22, 05/23, 05/24, 05/25 (SAB)
Original Effective Date: 06/22	**P&T Committee Meeting Date**: 04/22, 08/22, 06/23, 06/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications and some medically-accepted indications (as outlined in the required medical information section).

REQUIRED MEDICAL INFORMATION:
For initial authorization

1. One of the following:
    a. Trial and failure of at least eight weeks of therapy with a high-intensity statin therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily), defined as failure to achieve desired LDL-C lowering

    OR

    b. Documentation of statin intolerance, defined as one of the following:
        i. Rhabdomyolysis
        ii. Skeletal muscle related symptoms while on separate trials of at least two different statins, and resolution of symptoms after discontinuation
        iii. Elevated liver enzymes while on separate trials of at least two different statins with resolution after discontinuation

    OR

    c. The patient has an FDA labeled contraindication to a statin
2. Must meet listed criteria below for each specific diagnosis:
    a. For **familial hypercholesterolemia (FH),** one of the following must be met:

i. A "possible" or "definite" diagnosis of FH via Simon Broome criteria or a "probable" or "certain" diagnosis of FH via Dutch Lipid Clinic Network Criteria score of greater than or equal to 6 (see appendix)

OR

ii. Genetic mutation in one of the following genes: low-density lipoprotein receptors (LDLR), apolipoprotein B gene (APOB), or proprotein convertase subtilisin kexin type 9 (PCSK9), or ARH adaptor protein 1/LDLRAP1

OR

iii. LDL-C greater than 190 mg/dL (pretreatment or highest level while on treatment) and secondary causes have been ruled out. Secondary causes may include hypothyroidism, nephrosis, or extreme dietary patterns

OR

iv. Presence of xanthomas

b. For **ASCVD**, attestation of LDL-C greater than or equal to 70 mg/dL and history of clinical ASCVD, defined as one of the following:
   i. Acute coronary syndromes
   ii. History of myocardial infarction
   iii. Stable/unstable angina
   iv. Coronary or other arterial revascularization
   v. Stroke or transient ischemic attack
   vi. Peripheral artery disease presumed to be of atherosclerotic origin
   vii. Clinically significant coronary heart disease of atherosclerotic origin identified by diagnostic catheterization, imaging (CT angiogram or cardiac MRI), or stress testing (nuclear stress test or stress echocardiogram)

For initial reauthorization: Provider attestation of response to therapy, defined as a decrease in LDL-C levels from pre-treatment levels.

EXCLUSION CRITERIA:

- Concomitant use with another PCSK9 inhibitor
- Non-familial hyperlipidemia/hypercholesterolemia
- Primary prevention of ASCVD

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:

Initial authorization for one year. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Inclisiran (Leqvio®) is a double-stranded small interfering RNA (siRNA) that inhibits proprotein convertase subtilisin kexin type 9 (PCSK9) synthesis. The inhibition of PCSK9 results in increased numbers of LDLR on the surface of hepatocytes. LDLRs clear LDL-cholesterol from the blood; therefore, PCSK9 inhibitors reduce serum levels of LDL-C.

FDA APPROVED INDICATIONS:

Leqvio®:

- Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- Adjunct to diet and maximally tolerated statin therapy for treatment of adults with clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
- Limitations of use: the effect of inclisiran on cardiovascular morbidity and mortality has not been determined.

POSITION STATEMENT:

Inclisiran (Leqvio®) showed significant LDL-C lowering effects in clinical trials (39.7-51.3%) in addition to maximally tolerated statin therapy. Inclisiran was studied in three clinical phase 3 trials demonstrating that inclisiran compared to placebo as adjunct to maximally tolerated statin therapy reduces LDL-C in adults with HeFH (ORION-9 study) and in adults with ASCVD (ORION-10 and ORION-11). The cardiovascular outcomes trial for inclisiran, ORION-4, is not expected to be completed until 2026.

Familial hypercholesterolemia (FH) is typically diagnosed by either genetic testing or clinical presentation. A definitive diagnosis can be made with genetic mutations in any of the following genes: LDLR, APOB, or PCSK9. Clinical presentation involves many different patient factors. However, in the clinical trials for alirocumab, patients were diagnosed with definite FH using the Simon Broome criteria (see Appendix) or the World Health Organization/Dutch Lipid Network criteria (See Appendix). Severely elevated LDL-C levels and the presences or tendon xanthomas are typically diagnostic of FH.

REFERENCE/RESOURCES:

1. Leqvio Package insert. Novartis Pharmaceuticals Corporation. Dec. 2021.
2. Leqvio In: DRUGDEX® System [Internet database]. Ann Arbor, MI: Merative Micromedex. Updated periodically. Accessed May 8, 2025.
3. Leqvio In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed May 8, 2025.
4. 2018 AHA/ACC/AACVRP/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. Journal of the American College of Cardiology. 2019 Jun, 73 (24) e285-e350. Available at: https://www.jacc.org/doi/abs/10.1016/j.jacc.2018.11.003?_ga=2.130559624.666084477.1543267586-144035656.1543267586.
5. Ray, KK, Wright, RS, Kallend, D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. The New England Journal of Medicine. 2020; 382:1501-1519. Available at: https://www.nejm.org/doi/10.1056/NEJMoa1912387?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub 0pubmed.
6. Rall, FJ, Kallend D, Ray, KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. The New England Journal of Medicine. 2020; 382: 1520-1530. Available at: https://www.nejm.org/doi/10.1056/NEJMoa1913805?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub 0pubmed.
7. High cholesterol. Institute for Clinical and Economic Review (ICER). Public Meeting February 2021. Available at: https://icer.org/assessment/high-cholesterol-2021/. Accessed on February 25, 2022.

APPENDIX: Diagnostic Scoring Tools for familial hypercholesterolemia
Simon Broome criteria for FH

Diagnose a person with definite familial hypercholesterolemia (FH) if they have:

- Cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative
  OR
- Deoxyribonucleic acid (DNA)-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Diagnose a person with possible FH if they have cholesterol concentrations as defined in table 1 and at least one of the following.

- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.
- Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

Table 1. Cholesterol levels to be used as diagnostic criteria for the index individual levels either pre-treatment or highest on treatment

	Total cholesterol	LDL-C
Child/young person	> 6.7 mmol/L (260 mg/dL)	> 4.0 mmol/L (154 mg/dL)
Adults	> 7.5 mmol/L (290 mg/dL)	> 4.9 mmol/L (190 mg/dL)

World Health Organization (WHO)/Dutch Lipid Network criteria

Family history			
a	First degree relative known with premature (men<55 yrs, women <60yrs) coronary and vascular disease:		1
b	First degree relative known with LDL-cholesterol >95th percentile.		
	and/or		
a	First degree relative with tendon xanthomata and/or arcus cornealis.		2
b	Children below 18 yrs. with LDL-cholesterol >95th percentile.		
Clinical history			
a	Patient has premature (men<55 yrs, women <60yrs) CAD		2
b	Patient has premature (men<55 yrs, women <60yrs) cerebral or peripheral vascular disease.		1
Physical examination			
a	Tendon xanthomata		6
b	Arcus cornealis below the age of 45 yrs.		4
Laboratory analysis			
		mmol/l	mg/dl
a	LDL-cholesterol >8.5	>330	8
b	LDL-cholesterol 6.5 - 8.4	250-329	5
c	LDL-cholesterol 5.0 - 6.4	190-249	3
d	LDL-cholesterol 4.0 - 4.9 (HDL-cholesterol and triglycerides are normal)	155-189	1
DNA-analysis			
a	Functional mutation low-density lipoprotein receptor gene present		8

Diagnosis of FH is:

certain when	>8 points
probable when	6-8 points
possible when	3-5 points