Drug Coverage Policy

Effective Date.....8/15/2024
Coverage Policy Number..... IP0380
Policy Title.....Leqvio

Proprotein Convertase Subtilisin Kexin Type 9 Related Products – Leqvio

- Leqvio® (inclisiran subcutaneous injection – Novartis)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

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 statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).[1] The safety and effectiveness have not been established in pediatric patients.

Repatha® (evolocumab subcutaneous injection) and Praluent® (alirocumab subcutaneous injection) are PCSK9 inhibitor products.[2,3]

Dosing Information
Leqvio is given as a subcutaneous injection and should be administered by a healthcare professional.[1] The dose is 284 mg given as a single subcutaneous injection initially, again at 3 months, and then once every 6 months.

Guidelines
Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and atherosclerotic cardiovascular disease (ASCVD).[4-9] 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 cardiovascular (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 ≥ 50%.

- The **American College of Cardiology (ACC) Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.[4] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha or Praluent). Leqvio may be considered. For adults without clinical ASCVD or diabetes or LDL-C ≥ 190 mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is ≥ 1,000 Agatston units, PCSK9 monoclonal antibodies (i.e., Repatha or Praluent) may be non-statin agents to consider following high-intensity statin therapy and ezetimibe to achieve the goal of a ≥ 50% LDL-C reduction (and LDL-C threshold < 70 mg/dL).

- The **American Heart Association (AHA)/ACC guidelines on the management of blood cholesterol** (updated 2018) defines ASCVD as an acute coronary syndrome, those with a history of myocardial infarction, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[5,6] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.[5,6] Additionally, reviews have recognized that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[11-14]

- The **American Diabetes Association Standards of Care for Diabetes** discuss CV disease and risk management (2024).[7] For patients with diabetes who are 40 to 75 years of age at higher CV risk (including those with one or more ASCVD risk factors) it is recommended to use high-intensity statin therapy to reduce LDL-C by ≥ 50% of baseline and to target an LDL-C of < 70 mg/dL. Also, for patients with diabetes who are 40 to 75 years of age at higher CV risk, especially those with multiple ASCVD risk factors and an LDL-C ≥ 70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to a maximum tolerated statin.

- Guidelines for **Chronic Coronary Disease from the AHA and ACC** (along with other organizations) [2023] state in such patients who are judged to be at very high risk and on

maximally tolerated statin therapy and an LDL-C ≥ 70 mg/dL, ezetimibe can be beneficial to further reduce the risk of a major adverse coronary event.[8] Patients with chronic coronary disease who are considered to be at very high risk who have and LDL-C ≥ 70 mg/dL who are receiving maximally tolerated statins and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of a major adverse coronary event.

- A **Scientific Statement from the AHA on Familial Hypercholesterolemia** (2015),[9] as well as other information,[10] provide additional guidance on diagnosing familial hypercholesterolemia (e.g., HeFH). For HeFH, Dutch Lipid Network criteria scoring is used, as well the Simon Broome criteria.

Medical Necessity Criteria

Leqvio is considered medically necessary when ONE of the following is met (1, 2, or 3):

FDA-Approved Indications

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1. **Heterozygous Familial Hypercholesterolemia (HeFH).*** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a, b, or c):
       - **a)** Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
       - **b)** Patient has phenotypic confirmation of heterozygous familial hypercholesterolemia; OR
         Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.
       - **c)** Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting ONE of the following diagnostic criteria thresholds [(1) or (2)]:
         - **(1)** Prescriber confirms that the Dutch Lipid Network criteria score was > 5; OR
         - **(2)** Prescriber confirms that Simon Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient meets ALL of the following [(1), (2), and (3)]:
         - **(1)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND
         - **(2)** Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
         - **(3)** LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
       - **b)** Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
         - **(1)** 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 ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
         - **(2)** Patient meets ALL of the following [(a), (b), and (c)]:

(a) 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).
(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination product); AND
(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as a combination product) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient Currently Receiving Leqvio. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through Cigna, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

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2. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B): Note: This is not associated with established cardiovascular disease or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units [may require prior authorization]; OR

b) Patient has diabetes; AND

iii. Patient meets ONE of the following (a or b):

a) Patient meets ALL of the following [(1]), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND

(2) Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:

(1) 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 ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) 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).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination product); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as a combination product) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient Currently Receiving Leqvio. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through Cigna, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

Other Uses with Supportive Evidence

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3. Established Cardiovascular Disease.* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had one of the following conditions or diagnoses (a, b, c, d, e, or f):

a) A previous myocardial infarction or a history of an acute coronary syndrome; OR

b) Angina (stable or unstable); OR

c) A past history of stroke or transient ischemic attack; OR

d) Coronary artery disease; OR

e) Peripheral arterial disease; OR

f) 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.

iii. Patient meets ONE of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
(3) Low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 55 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
(1) 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 ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
(2) Patient meets ALL of the following [(a), (b), and (c)]:
(a) 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).
(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination product); AND
(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as a combination product) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient Currently Receiving Leqvio. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through Cigna, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Dosing. Approve ONE of the following dosage regimens (A or B):
A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR
B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

Note:
* A patient may have a diagnosis that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia may have established cardiovascular disease, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

Employer Plans:

Product	Criteria
Leqvio (inclisiran)	**1.** Approve for 1 year if the patient meets BOTH of the following (A and B): **A)** Patient meets the above medical necessity criteria; AND **B)** Patient meets BOTH of the following (i and ii): **i.** Patient has tried Repatha (evolocumab subcutaneous injection) [may require prior authorization]; AND **ii.** Patient has experienced inadequate efficacy or significant intolerance, according to the prescriber.

Individual and Family Plans:

Product	Criteria
Leqvio (inclisiran)	**1.** Approve for 1 year if the patient meets BOTH of the following (A and B): **A)** Patient meets the above medical necessity criteria; AND **B)** Patient meets BOTH of the following (i and ii): **i.** Patient has tried Repatha (evolocumab subcutaneous injection) [may require prior authorization]; AND **ii.** Patient has experienced inadequate efficacy or significant intolerance, according to the prescriber.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1306	Injection, inclisiran, 1 mg

References

1. Leqvio® subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis; July 2023.
2. Repatha® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; September 2021.
3. Praluent® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron; March 2024.
4. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 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.* 2022;80(14):1366-1418.
5. 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. *Circulation*. 2014;129(25 Suppl 2):S1-S45.
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7. American Diabetes Association Professional Practice Committee. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S179-S218.
8. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2023;82(9):833-955.
9. 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.
10. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2012;23:282-289.
11. Hect HS, Cronin P, Blaha M, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Thorac Imaging*. 2017;32(5):W54-S66.
12. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72(4):434-447.
13. Razavi AC, Agatston AS, Shaw LJ, et al. Evolving role of calcium density in coronary artery calcium scoring and atherosclerotic cardiovascular disease risk. *JACC Cardiovas Imaging*. 2022;15:1648-1662.
14. Lehker A, Mukherjee D. Coronary calcium risk score and cardiovascular risk. *Curr Vasc Pharmacol*. 2021;19(3):280-284.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** policy title from Inclisiran to Proprotein Convertase Subtilisin Kexin Type 9 Related Products – Leqvio. **All Indications**: Clarified "Initial Therapy" versus "Currently Receiving Leqvio" criteria and added additional examples of what is considered a response to therapy; Removed "Use is adjunctive to diet and maximally tolerated statin therapy [unless contraindicated or intolerant"; Updated the statin intolerance criteria, to clearly define what is considered statin intolerant, with notes and examples also included; Added dosing to the policy; Added a Note: * A patient may have a diagnosis that pertains to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia may have established cardiovascular disease, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia). **Heterozygous Familial Hypercholesterolemia:** For Initial Therapy, The specialist physician requirement was removed. For the requirement that the patient has had 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 was changed to state that the patient has had phenotypic confirmation of heterozygous familial hypercholesterolemia and the above examples moved to a Note. **Primary Hyperlipidemia:** For Initial Therapy, the specialist physician requirement was removed. Removed "Individual has a coronary artery calcium or calcification score of 100 or greater Agatston units or 75th percentile or greater for the individual's age, gender and ethnicity [coronary calcium scan may require prior authorization] OR Calculated 10 year ASCVD risk score of 7.5% or higher and replaced with "Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units OR Patient has diabetes". Added a requirement that "Patient has tried the one high-intensity statin therapy (atorvastatin or rosuvastatin) along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks". The requirement that the low-density lipoprotein cholesterol level after treatment	8/15/2024

	with one high-intensity statin therapy, along with ezetimibe, be ≥ 100 mg/dL was changed to ≥ 70 mg/dL. **Established Cardiovascular Disease:** The name of the indication was changed to as stated (previously "Atherosclerotic Cardiovascular Disease"). For Initial Therapy, the specialist physician requirement was removed. The requirement that the low-density lipoprotein cholesterol level after treatment with one high-intensity statin therapy be ≥ 70 mg/dL was changed to ≥ 55 mg/dL.	

The policy effective date is in force until updated or retired.

APPENDIX A

Simon Broome Register Diagnostic Criteria.[9,10]

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.[9,10]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Patient is < 18 years of age with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA Analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

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.