PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexletol Prior Authorization Policy
- Nexletol® (bempedoic acid tablets – Esperion)

REVIEW DATE: 05/08/2024

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 NATIONAL FORMULARY COVERAGE:

OVERVIEW

Nexletol, an adenosine triphosphate-citrate lyase inhibitor, is indicated for the following uses:[1]

- To reduce the risk of myocardial infarction (MI) and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with either: 1) **established cardiovascular disease** (CVD), or 2) **at high risk for a CVD event but without established CVD**.
- **Primary hyperlipidemia**, including **heterozygous familial hypercholesterolemia** (HeFH), in adults as an adjunct to diet, in combination with other low-density lipoprotein cholesterol (LDL-C) lowering therapies, or alone when concomitant LDL-C lowering therapy is not possible, to reduce LDL-C.

The safety and effectiveness have not been established in pediatric patients.[1]

Clinical Efficacy

CLEAR Outcomes was a randomized, double-blind, placebo-controlled trial involving 13,970 adults, 18 to 85 years of age who were unable or unwilling to take statins due to unacceptable adverse events. Patients had or were at high risk for CVD.[1,2] Patients without established CVD were considered high risk for CVD based on meeting at least one of the following: diabetes mellitus (type 1 or type 2) in females > 65 years of age or males > 60 years of age; a Reynolds Risk score > 30% or a SCORE Risk score > 7.5% over 10 years; or a coronary artery calcium score > 400 Agatston units at any time in the past.[1] Patients were assigned to receive Nexletol or placebo.[1,2] Use of statins at very low doses were

permitted, as well as other lipid lowering therapies (e.g., ezetimibe, bile acid sequestrants, fibrates). The mean patient age was 65 years. In total, 70% of patients had a previous cardiovascular (CV) event (secondary prevention population) whereas 30% of patients were categorized as being in the primary prevention group. In total, 38% of patients were receiving at least one lipid-modifying therapy. At baseline, 23% of patients were utilizing a statin and 12% of patients were on ezetimibe. The mean LDL-C at baseline was 139 mg/dL. The median follow-up was 40.6 months. The mean LDL-C level after 6 months of treatment with Nexletol was 107 mg/dL vs. 136 mg/dL for placebo. The primary endpoint (death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization) occurred in 11.7% of patients in the Nexletol group vs. 13.3% of patients in the placebo group (P = 0.004). The composite endpoint (death from CV causes, nonfatal stroke, or nonfatal MI) occurred in 8.2% of patients given Nexletol vs. 9.5% of patients in the placebo group (P = 0.006).

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.[3-11] 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 ≥ 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.[3] 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 (or non-high-density lipoprotein cholesterol [HDL-C] < 85 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 proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody (i.e., Repatha® [evolocumab subcutaneous injection] or Praluent® [alirocumab subcutaneous injection]). Nexletol can be considered after these therapies.
- The **American Heart Association (AHA)/ACC** guidelines on the management of blood cholesterol (2018) define patients with ACSVD as those with acute coronary syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[4,5] An LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Guidelines and 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.[13-16]
- The **American Diabetes Association Standards of Care for Diabetes** discuss CV disease and risk management (2024).[8] 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. In patients with diabetes intolerant to statin therapy, treatment with Nexletol is recommended to reduce CV event rates as an alternative cholesterol-lowering plan.
- 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 with an LDL-C ≥ 70 mg/dL,

ezetimibe can be beneficial to further reduce the risk of a major adverse coronary event.[9] Patients with chronic coronary disease who are considered to be at very high risk who have an 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. In patients with chronic coronary disease who are on maximally tolerated statin therapy who have an LDL-C ≥ 70 mg/dL and in whom ezetimibe and a PCSK9 monoclonal antibody are not adequate or are not tolerated, it may be reasonable to add Nexletol.

- The **American Association of Clinical Endocrinologists and American College of Endocrinology** has guidelines regarding the management of dyslipidemia and the prevention of CV disease (2020).[7] Nexletol is cited as an option for intensification of therapy after use of standard agents such as high-intensity/moderate-intensity statins.
- The **International Lipid Expert Panel** published a position paper in 2023 on use of Nexletol in the management of lipid disorders and CV risk.[10] One recommendation is that in patients with statin intolerance, Nexletol monotherapy, or in combination with ezetimibe and other non-statin drugs is recommended to enable patients to achieve therapeutic goals. In primary prevention, Nexletol may be considered for patients at high and very high CV risk who, despite optimally maximally tolerated doses of statins and ezetimibe are not achieving target LDL-C levels.
- **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[11] 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%.[11] Other information also provides guidance on the diagnosis of HeFH.[12]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nexletol. All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Nexletol for the requested indication under the Coverage Review Department and is currently receiving Nexletol is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Nexletol, or is restarting Nexletol, Initial Therapy criteria must be met.

- **Nexletol® (bempedoic acid tablets (Esperion)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **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, and iii):
     - **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 above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
(3) Low-density lipoprotein cholesterol 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]); OR
(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 products); AND
(c) 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); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexletol. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (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 Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

2. 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, and iii):
- **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 above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
    - **(3)** Low-density lipoprotein cholesterol 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]); OR
    - **(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 products); AND
      - **(c)** 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); OR
        Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

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

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (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 Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

3. 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, and iii):
- **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; 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 products); AND
      - **(c)** 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); OR
        Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexletol. According to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (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 Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

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).

CONDITIONS NOT COVERED

- **Nexletol® (bempedoic acid tablets (Esperion)**

is(are) considered experimental, investigational, or unproven for ANY other use(s).

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	It was added to the Policy Statement that a patient who has previously met initial therapy criteria for Nexletol for the requested indication under the Coverage Review Department and is currently receiving Nexletol is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Nexletol, or is restarting Nexletol, initial criteria must be met. In addition, the following changes were made: **Atherosclerotic Cardiovascular Disease:** Requirements were divided to distinguish between initial therapy and patient currently receiving Nexletol (previously there was only one criterion set). For a patient who is currently receiving Nexletol and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met, which was newly developed. The continuation of therapy criteria states that according to the prescriber, the patient has experienced a response to therapy with examples provided in a Note. **Heterozygous Familial Hypercholesterolemia:** Requirements were divided to distinguish between initial therapy and patient currently receiving Nexletol (previously there was only one criterion set). The criteria to confirm the diagnosis of heterozygous familial hypercholesterolemia were reworded regarding the use of the Dutch Lipid Network criteria and the Simon Broome criteria; also, the phrase "prescriber used" was changed to "the prescriber confirms." For a patient who is currently receiving Nexletol and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy	04/26/2023 (criteria changes done with Selected Revision changes on 05/03/2023).

	criteria has to be met, which was newly developed. The continuation of therapy criteria states that according to the prescriber, the patient has experienced a response to therapy with examples provided in a Note.	
Selected Revision	**Atherosclerotic Cardiovascular Disease:** A Note was added that a patient may have diagnoses that pertain to more than one indication, therefore, consider review under different approval conditions, if applicable. **Heterozygous Familial Hypercholesterolemia:** A Note was added that a patient may have diagnoses that pertain to more than one indication, therefore, consider review under different approval conditions, if applicable. **Primary Hyperlipidemia:** This was a new indication added under Other Uses with Supportive Evidence.	05/03/2023
Update	01/03/2024: No criteria change. Updated the wording of the indication.	NA
Selected Revision	**Atherosclerotic Cardiovascular Disease:** Coronary artery disease was added as a condition or diagnosis that represents this indication of use in this related requirement.	01/17/2024
Annual Revision	**Established Cardiovascular Disease:** The name of the indication was changed to as stated (previously "Atherosclerotic Cardiovascular Disease"). For Initial Therapy, the requirement that the low-density lipoprotein cholesterol level after treatment with one high-intensity statin therapy and ezetimibe be ≥ 70 mg/dL was changed to ≥ 55 mg/dL. **Heterozygous Familial Hypercholesterolemia:** For Initial Therapy, the requirement that the 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 was changed to state that the patient has phenotypic confirmation of heterozygous familial hypercholesterolemia and the above examples were moved to a Note. **Primary Hyperlipidemia:** This indication was moved from the "Other Uses with Supportive Evidence" section to the "FDA-Approved Indications" section. For Initial Therapy, a patient with diabetes now qualifies for this indication (if requirements are met); previously, high risk was only defined as a patient who had a "coronary artery calcium or calcification score ≥ 300 Agatston units". The requirement that the low-density lipoprotein cholesterol level after treatment with one high-intensity statin therapy, along with ezetimibe, be ≥ 100 mg/dL was changed to ≥ 70 mg/dL.	05/08/2024

APPENDIX A

Simon Broome Register Diagnostic Criteria.[11,12]

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.[11,12]

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.