Reference number(s)
5120-A

STANDARD MEDICARE PART B MANAGEMENT

LEQVIO (inclisiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Leqvio 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).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Current LDL-C level for both initial requests and continuation requests. The level must be dated within six months preceding the authorization request.
B. For members with clinical atherosclerotic cardiovascular disease (ASCVD), chart notes confirming clinical ASCVD (See Appendix A).
C. For members without clinical atherosclerotic cardiovascular disease (ASCVD), untreated (before any lipid lowering therapy) LDL-C level.
D. If member has contraindication or intolerance to statins, chart notes confirming the contraindication or intolerance (See Appendix B and C).

III. CRITERIA FOR INITIAL APPROVAL

Primary hyperlipidemia
Authorization of 6 months may be granted for treatment of primary hyperlipidemia when one of the following criteria is met:
A. Member meets all of the following:
    1. Member has a history of clinical atherosclerotic cardiovascular disease (ASCVD) (See Appendix A).
    2. Member meets one of the following:
        i. Current LDL-C level ≥ 70 mg/dL after at least three months of treatment with a high-intensity statin. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used.
        ii. Current LDL-C level ≥ 70 mg/dL with a contraindication or intolerance to statins (See Appendix B and C).

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3. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (See Appendix B and C).

B. Member meets all of the following:
   1. Member had an untreated (before any lipid-lowering therapy) LDL-C level ≥ 190 mg/dL in the absence of a secondary cause.
   2. Member meets one of the following:
      i. Current LDL-C level ≥ 100 mg/dL after at least three months of treatment with a high-intensity statin. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used.
      ii. Current LDL-C level ≥ 100 mg/dL with a contraindication or intolerance to statins (See Appendix B and C).
   3. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (See Appendix B and C).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Leqvio.
B. Leqvio is being used to treat an indication enumerated in Section III.
C. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (See Appendix B and C).
D. The member is receiving benefit from therapy. Benefit is defined as achievement or maintenance of an LDL-C reduction (e.g., LDL-C is now at goal, robust lowering of LDL-C).

V. APPENDICES

APPENDIX A. Clinical ASCVD
- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease (PAD) of presumed atherosclerotic origin (e.g., carotid artery stenosis, lower extremity PAD)
- Obstructive coronary artery disease (defined as fifty percent or greater stenosis on cardiac computed tomography angiogram or catheterization)
- Coronary Artery Calcium (CAC) Score ≥ 1000

APPENDIX B. Statin-associated muscle symptoms (SAMS) and statin re-challenge
- Score of 7 or higher on the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)
- Statin-associated elevation in creatine kinase (CK) level ≥ 10 times upper limit of normal (ULN)
  NOTE: Statin re-challenge is NOT required for members who have experienced an elevation of CK level ≥10 times ULN after receiving lipid-lowering therapy (LLT) with a statin.

APPENDIX C. Contraindications to statins

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- Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase (ALT) level ≥ 3 times ULN)
- Pregnancy or planned pregnancy
- Breastfeeding

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Leqvio.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia from the American Heart Association
4. National Lipid Association recommendations for patient-centered management of dyslipidemia
5. 2018 AHA/ACC guideline on the management of blood cholesterol: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
6. 2022 American College of Cardiology Expert Consensus Decision Pathway on the Role of Nonstatin therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leqvio and are included.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

In 3 large, randomized studies, inclisiran significantly reduced LDL-C compared with placebo in patients who were on maximally tolerated statin doses but still required LDL-C lowering.

Support for using Leqvio in patients with heterozygous familial hypercholesterolemia is found in the package insert and the ORION-9 trial. The ORION-9 randomized trial (N=482) compared inclisiran with placebo in adults with heterozygous familial hypercholesterolemia and elevated LDL-C despite maximally tolerated doses of statin therapy with or without ezetimibe; patients receiving a PCSK9 monoclonal antibody were excluded. Patients were administered Leqvio as a subcutaneous injection on days 1, 90, 270 and 450. Patients had an LDL-C of at least 100 mg/dL (2.6 mmol/L). Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-39.7% vs +8.2%; difference, -47.9 percentage points; 95% CI, -53.5 to -42.3); mean absolute change in LDL-C levels was -59 versus +9.9 mg/dL (-1.5 vs +0.3 mmol/L). The time-averaged percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-38.1% vs +6.2%; difference, -44.3 percentage points; 95% CI, -48.5 to -40.1); mean absolute change was -56.9 vs +5.8 mg/dL (-1.5 vs +0.1 mmol/L). The percent change in PCSK9 level from baseline at day 510 was significantly greater with inclisiran versus placebo (-60.7% vs +17.7%); mean absolute change was -282.6 vs +54.5 mcg/L. Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-26.1% vs +6.8%), apolipoprotein B (-34% vs +2.9%), and non-HDL-C (-36.1% vs +7.5%). An LDL-C goal of less than 100 mg/dL was achieved by 65.3% versus 8.8% for inclisiran versus placebo and an LDL-C goal of less than 70 mg/dL was achieved by 40.8% with inclisiran versus 1.3% with placebo. Among 432 patients who had genetic testing, 80.8% had single LDLR variants,

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5.3% had APOB variants, and 8.6% had a variant in LDLR and either APOB or PCSK9. Patients with LDLR variants had the highest mean baseline LDL-C level (160.8 mg/dL [4.2 mmol/L]). There were significant differences in mean percent change in LDL-C with inclisiran versus placebo from baseline at day 510 in patients with LDLR pathogenic variants (n=231; difference, -46 percentage points), LDLR probably pathogenic variants (n=17; difference, -48.3 percentage points), LDLR variants of uncertain significance (n=8; difference, -42.3 percentage points), APOB variants (n=23; difference, -52.1 percentage points), 2 variants (n=37; difference, -41.2 percentage points), no variants (n=115; difference, -59.2 percentage points), and no genetic testing (n=50; difference, -46.8 percentage points). There were no significant differences between inclisiran and placebo in the incidence of adverse events (76.8% vs 71.7%), but serious adverse events were significantly less frequent with inclisiran (7.5% vs 13.8%). Injection site reactions were more frequent with inclisiran (17% vs 1.7%) but were mostly mild.

The ORION-10 randomized trial (N=1561) compared inclisiran with placebo in adults with atherosclerotic cardiovascular disease (ASCVD) and elevated LDL-C despite maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy; patients receiving a PCSK9 monoclonal antibody were excluded. Patients had an LDL-C of at least 70 mg/dL (1.8 mmol/L). Inclisiran 284 mg was administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450. Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-51.3% vs +1%; difference, -52.3 percentage points; 95% CI, -55.7 to -48.8); mean absolute change was -56.2 versus -2.1 mg/dL (-1.45 vs -0.05 mmol/L). The time-adjusted percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-51.3% vs +2.5%; difference, -53.8 percentage points; 95% CI, -56.2 to -51.3); mean absolute change was -53.7 vs -0.4 mg/dL (-1.39 vs -0.01 mmol/L). The percent change in PCSK9 levels from baseline at day 510 was significantly greater with inclisiran versus placebo (-69.8% vs +13.5%). Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-33.6% vs +0.4%), apolipoprotein B (-44.8% vs -1.7%), non-HDL-C (-47.4% vs -0.1%). LDL-C goals of less than 70 mg/dL and less than 100 mg/dL were achieved in 74.4% and 83.4% of inclisiran-treated patients compared with 15.3% and 49.6% of placebo-treated patients. There were no significant differences between inclisiran and placebo in the incidence of adverse events (73.5% vs 74.8%) or serious adverse events (22.4% vs 26.3%). Injection site reactions were more frequent with inclisiran (2.6% vs 0.9%) but were mostly mild.

The ORION-11 randomized trial (N=1617) compared inclisiran with placebo in adults with ASCVD (approximately 87.5%) or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or 10-year risk of cardiovascular event of at least 20% on Framingham Risk Score). Patients had elevated LDL-C despite maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy, and patients receiving a PCSK9 monoclonal antibody were excluded. Patients with ASCVD had an LDL-C of at least 70 mg/dL (1.8 mmol/L), and patients with an ASCVD risk equivalent had an LDL-C of at least 100 mg/dL (2.6 mmol/L). Inclisiran 284 mg was administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450. Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-45.8% vs +4%; difference, -49.9 percentage points; 95% CI, -53.1 to -46.6); mean absolute change was -50.9 versus +1 mg/dL (-1.32 vs +0.03 mmol/L). The time-adjusted percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-45.8% vs +3.4%; difference, -49.2 percentage points; 95% CI, -51.6% to -46.8%); mean absolute change was -48.6 vs +0.3 mg/dL (-1.26 vs +0.01 mmol/L). The percent change in PCSK9 levels from baseline at day 510 was significantly greater with inclisiran versus placebo (-63.6% vs +15.6%). Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-28% vs +1.8%), apolipoprotein B (-38.2% vs +0.8%), and non-HDL-C (-41.2% vs +2.2%). LDL-C goals of less than 70 mg/dL and less than 100 mg/dL were achieved in 69.6% and 81.6% of inclisiran-treated patients compared with 12.9% and 52.7% of placebo-treated patients. There were no significant differences between inclisiran and placebo in the incidence of adverse events (82.7% vs 81.5%) or serious adverse events (22.3% vs 22.5%). Injection site reactions were more frequent with inclisiran (4.7% vs 0.5%) but were mostly mild.

VIII.REFERENCES

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