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Subject: Inclisiran (Leqvio®) Injection

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DESCRIPTION:

Inclisiran (Leqvio) injection was initially approved by the U.S. Food and Drug Administration (FDA) in December 2021 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). The effect of inclisiran on cardiovascular morbidity and mortality has not yet been determined. The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently underway, and their completion is anticipated in 2026 and 2027, respectively. In July 2023, the FDA approved indication was expanded based on updated results from the ORION-11 trial that included patients with ASCVD-risk equivalents. The new indication is “as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including HeFH, to reduce LDL-C”. Inclisiran, as sponsor by the innovator drug company, was granted orphan drug designation by the FDA for the treatment homozygous familial hypercholesterolemia (HoFH) in January 2018. Inclisiran is a double-stranded small interfering RNA (siRNA) conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

The efficacy of inclisiran was investigated in three randomized, double-blind, placebo-controlled trials that enrolled 3,660 adults with HeFH, clinical ASCVD, or increased risk for ASCVD, who were taking maximally tolerated statin therapy and who required additional LDL-C lowering. Patients taking PCSK9 inhibitors were excluded from the trials. Study 1 (ORION-10) looked at LDL-C reduction in patients with ASCVD, Study 2 (ORION-11) in patients with ASCVD or increased risk for ASCVD, and Study 3 (ORION-9) in patients with HeFH. All three studies had the primary efficacy outcome measure of change from baseline to day 510 in LDL-C. Study 1 participants had a mean baseline LDL-C of 105 mg/dL, and the

difference between Leqvio and placebo in mean percentage change from baseline was -52%. Study 2 participants had a mean baseline LDL-C of 105 mg/dL, and the difference between Leqvio and placebo in mean percentage change from baseline was -50%. Study 3 participants had a mean baseline LDL-C of 153 mg/dL, and the difference between Leqvio and placebo in mean percentage change from baseline was -48%.

Heterozygous familial hypercholesterolemia (HeFH)

Criteria have been developed to aid in diagnosing HeFH. These include the Simon Broome Register criteria and Dutch Lipid Clinic Network criteria. A definite diagnosis of HeFH according to Simon Broome diagnostic criteria requires one of the following:

- Total cholesterol greater than 6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/L in a child/young person, or greater than 7.5 mmol/L or LDL-C greater than 4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) **and** tendon xanthomas, or evidence of these signs in a first-degree relative (parent, sibling or child), or second-degree relative (e.g., grandparent, uncle or aunt)

  OR

- DNA-based evidence of an LDL receptor mutation, familial defective Apo B-100, or a PCSK9 mutation

A possible diagnosis of HeFH according to Simon Broome diagnostic criteria requires the following:

- Total cholesterol greater than 6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/L in a child/young person, or greater than 7.5 mmol/L or LDL-C greater than 4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment)
  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

    OR

  - 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

The Dutch Lipid Clinic Network criteria assign points based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score is attributed to each component; the higher the score, the higher the likelihood of the person having HeFH. A definitive diagnosis of HeFH can be made in patients with greater than 8 points. A probable diagnosis can be made in patients with 6 to 8 points. Although the Simon Broome Register criteria consider a molecular diagnosis as evidence for definite FH, the Dutch Lipid Clinic Network requires that at least one other criterion be met in addition to molecular diagnosis.

Table: Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolemia

Group 1: Family history	Points
• First-degree relative with known premature (less than 55 years, men; less than 60 years, women) coronary heart disease (CHD)	1

• First-degree relative with known LDL cholesterol greater than 95th percentile by age and gender for country	1
• First-degree relative with tendon xanthoma and/or corneal arcus	2
• Children less than 18 years with LDL cholesterol greater than 95th percentile by age and gender for country	2
Group 2: Clinical history	**Points**
• Subject has premature (less than 55 years, men; less than 60 years, women) CHD	2
• Subject has premature (less than 55 years, men; less than 60 years, women) cerebral or peripheral vascular disease	1
Group 3: Physical examination	**Points**
• Tendon xanthoma	6
• Corneal arcus in a person less than 45 years	4
Group 4: Biochemical results (LDL-C)	**Points**
• Greater than 8.5 mmol/L (greater than 330 mg/dL)	8
• 6.5–8.4 mmol/L (250–329 mg/dL)	5
• 5.0–6.4 mmol/L (190–249 mg/dL)	3
• 4.0–4.9 mmol/L (155–189 mg/dL)	1
Group 5: Molecular genetic testing (DNA analysis)	**Points**
• Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
Use and Interpretation	
Assign only one score, the highest applicable, per group then add the points from each group to achieve the total score: • Definitive FH diagnosis: greater than 8 points • Probable FH diagnosis: 6 to 8 points • Possible FH diagnosis: 3 to 5 points • Unlikely FH diagnosis: 0 to 2 points	

Atherosclerotic Cardiovascular Disease (ASCVD) – Secondary Prevention

The most recent 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of Blood Cholesterol states that clinical atherosclerotic cardiovascular disease (ASCVD) includes the following, all of atherosclerotic origin:

- Acute coronary syndrome (ACS)
- History of myocardial infarction (MI)

- Stable or unstable angina
- Coronary or other arterial revascularization
- Stroke
- Transient ischemic attack (TIA)
- Peripheral artery disease (PAD) including aortic aneurysm

Management

The 2022 American College of Cardiology (ACC) Consensus Decision Pathway was designed to address current gaps in care for LDL-C lowering to reducing ASCVD risk. This effort relies extensively on the evidence established by the 2013 ACC/AHA and 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, and provides further recommendations regarding the use of newer non-statin therapies. The key updates that the 2022 ACC Consensus Pathway recommends for patients with ASCVD on maximally tolerated statin therapy are a recommendation for a lower LDL-C threshold of 55 mg/dL (or non-HDL-C of 85 mg/dL) for adults with ASCVD at very high risk, and an LDL-C threshold of 70 mg/dL (or non-HDL-C of 100 mg/dL) for adults with ASCVD not at very high risk when considering the addition of a non-statin therapy. If adults with clinical ASCVD at very high risk on a statin therapy for secondary prevention require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin therapy.

The 2022 ACC Consensus Panel also released updated Expert Consensus Decision Pathways (ECDPs) to encourage clinicians to consider a range of important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy including when to consult a lipid specialist. Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve a reduction of LDL-C ≥50% and LDL-C <70 mg/dL (or non–HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with non-statin therapy (ezetimibe, PCSK9 inhibitors, bempedoic acid, and/or inclisiran).

The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol categorizes high intensity statin therapy as atorvastatin 40 to 8 0mg and rosuvastatin 20 to 40 mg which provides an LDL-C lowering of greater than or equal to 50%.

The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol states the following regarding PCSK9 therapy:

- Primary severe hypercholesterolemia (LDL-C greater than or equal to 190 mg/dL [greater than or equal to 4.9 mmol/L])
    - In patients 30 to 75 years of age with HeFH and with an LDL-C level of 100 mg/dL or higher (greater than or equal to 2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered
    - In patients 40 to 75 years of age with an untreated LDL-C level of 220 mg/dL or higher (greater than or equal to 5.7 mmol/L) or an LDL-C that is greater than or equal to 130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered

- Secondary atherosclerotic cardiovascular disease (ASCVD) prevention
    - In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe

The National Lipid Association (NLA) 2019 consensus statement identifies the following patients, who are already on maximally tolerated statin therapy, as most likely to benefit from PCSK9 therapy.

- Extreme high-risk (greater than or equal to 40% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 70 mg/dL and either of the following:
    - Extensive or active burden of ASCVD (i.e., polyvascular ASCVD, which affects all 3 vascular beds - coronary, cerebrovascular, and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multivessel coronary artery disease defined as greater than or equal to 40% stenosis in greater than or equal to 2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors
    - Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (i.e., HeFH, diabetes, LDL-C greater than or equal to 100 mg/dL, less than high–intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high-sensitivity C-reactive protein greater than 3 mg/L, or metabolic syndrome, usually occurring with other extremely high–risk or very-high-risk characteristics), usually with other adverse or poorly controlled cardiometabolic risk factors present. Patients with ASCVD and HeFH or severe hyperlipidemia (SH) LDL-C greater than or equal to 220 mg/dL are an additional group of extremely high–risk patients, with greater than or equal to 45% 10-year ASCVD risk despite statin therapy. Statin-treated HeFH patients with coronary artery calcium (CAC) score greater than 100 Agatston units also have about a 45% 10-year ASCVD risk despite statin therapy
- Very high-risk (30 to 39% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 100 mg/dL and the following:
    - Less-extensive clinical ASCVD (i.e., no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event greater than or equal to 2 years prior, and no coronary artery bypass grafting)
    - Adverse or poorly controlled cardiometabolic risk factor(s) including age greater than or equal to 65 years, current smoking, chronic kidney disease, lipoprotein(a) greater than or equal to 37 nmol/L, high-sensitivity C-reactive protein 1 to 3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors
- High-risk (20 to 29% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 130 mg/dL and either of the following:
    - High-risk patients with ASCVD who have the following:
        - Less-extensive ASCVD
        - Well-controlled cardiometabolic risk factors (i.e., no diabetes, nonsmoker, on high-intensity statin with LDL-C less than 100 mg/dL, blood pressure less than 140/90 mm Hg, and C-reactive protein less than 1 mg/dL)

- Primary prevention patients with HeFH or SH LDL-C greater than or equal to 220 mg/dL and have the following:
  - No clinical ASCVD or CAC less than 100 Agatston units
  - Poorly controlled cardiometabolic risk factor

CAC Agatston score in non-contrast CT can be used for patient risk classification for coronary heart disease:

- 0 CAC - no CAC, very low risk,
- 1 to 99 CAC - mild CAC, mildly increased risk
- 100 to 299 CAC - moderate CAC, moderately increased risk
- greater than or equal to 300 CAC moderate to severely increased risk

POSITION STATEMENT:

Initiation of inclisiran (Leqvio) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. The member has a diagnosis of **ANY** of the following ("a", "b", "c", "d"', or "e"):
   a. Heterozygous familial hypercholesterolemia (HeFH), **AND** the member has **ANY** of the following:
      i. Genetic confirmation of one mutant allele at the *LDLR*, *Apo-B*, *PCSK9 or* ARH adaptor protein (*LDLRAP1*) gene
      ii. Pretreatment LDL-C greater than 190 mg/dL (greater than 4.9 mmol/L)
      iii. Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea)
      iv. "Definite" or "possible" familial hypercholesterolemia as defined by the Simon Broome criteria
      v. A Dutch Lipid Clinic Network Criteria score of greater than 5
      vi. A treated LDL-C level greater than or equal to 100 mg/dL after treatment with statin treatment with or without ezetimibe but prior to Leqvio therapy
   b. Clinical atherosclerotic cardiovascular disease (ASCVD), **AND** the member has **ANY** of the following:
      i. Acute coronary syndrome
      ii. History of myocardial infarction
      iii. Stable or unstable angina
      iv. Coronary or other arterial revascularization
      v. History of stroke
      vi. History of transient ischemic attack
      vii. Peripheral arterial disease, including aortic aneurysm, presumed to be of atherosclerotic origin

c. Primary hyperlipidemia, **AND EITHER** of the following ("i" or "ii"):

   i. The member has a coronary artery calcium or calcification (CAC) score greater than or equal to 300 Agatston units

   ii. The member has a pre-treatment LDL-C level greater than or equal to 190 mg/dL (greater than or equal to 4.9 mmol/L)

d. A greater than or equal to 20% 10-year ASCVD risk, **AND ANY** of the following ("i", "ii", or "iii"):

   i. The member has greater than or equal to 40% 10-year ASCVD risk, **AND BOTH** of the following ("1" and "2"):

      1. LDL-C greater than or equal to 70 mg/dL while on maximally tolerated statin therapy

      2. **ONE** of the following ("a", "b", or "c"):

         a. The member has extensive or active burden of ASCVD (i.e., polyvascular ASCVD, which affects all 3 vascular beds - coronary, cerebrovascular, and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multivessel coronary artery disease defined as greater than or equal to 40% stenosis in greater than or equal to 2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors.

         b. Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (i.e., diabetes, LDL-C greater than or equal to 100 mg/dL, less than high–intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high-sensitivity C-reactive protein greater than 3 mg/L, or metabolic syndrome, usually occurring with other extremely high–risk or very-high-risk characteristics), usually with other adverse or poorly controlled cardiometabolic risk factors present.

         c. Members with ASCVD and LDL-C greater than or equal to 220 mg/dL with greater than or equal to 45% 10-year ASCVD risk despite statin therapy.

   ii. The member has 30 to 39% 10-year ASCVD risk, **AND ALL** of the following ("1", "2", and "3"):

      1. LDL-C greater than or equal to 100 mg/dL while on maximally tolerated statin therapy

      2. Less-extensive clinical ASCVD (i.e., no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event greater than or equal to 2 years prior, and no coronary artery bypass grafting)

      3. Adverse or poorly controlled cardiometabolic risk factor(s) including age 65 years or older, current smoking, chronic kidney disease, lipoprotein(a) greater than or equal to 37 nmol/L, high-sensitivity C-reactive protein 1 to 3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors

   iii. The member has 20 to 29% 10-year ASCVD risk, **AND BOTH** of the following ("1" and "2"):

      1. LDL-C greater than or equal to 130 mg/dL while on maximally tolerated statin therapy

      2. **ONE** of the following ("a" or "b"):

a. The member has less extensive ASCVD and well-controlled cardiometabolic risk factors (i.e., no diabetes, nonsmoker, on high-intensity statin with LDL-C less than 100 mg/dL, blood pressure less than 140/90 mm Hg, and C-reactive protein less than 1 mg/dL)

b. The use is for primary prevention with LDL-C greater than or equal to 220 mg/dL, **AND BOTH** of the following ("i" and "ii'):

i. No clinical ASCVD or CAC less than 100 Agatston units

ii. Poorly controlled cardiometabolic risk factor

e. Another FDA-approved indication for inclisiran subcutaneous injection

2. **EITHER** of the following ("a" or "b"):

a. The member's age is within FDA labeling for the requested indication for inclisiran

b. The prescriber has provided information in support of using inclisiran for the member's age for the requested indication

3. **ANY** of the following ("a", "b", or "c"):

a. Member has tried and had an inadequate response to a PCSK9 inhibitor [e.g., Repatha (evolocumab), Praluent (alirocumab)] after at least 8 continuous weeks of treatment – prior use of a PCSK9 inhibitor must be confirmed by either submission of medical records or assessment of claims history in the past year

b. Member has an intolerance or hypersensitivity to PCSK9 inhibitor therapy – the member's specific intolerance or hypersensitivity must be provided

c. Member has an FDA-labeled contraindication to **ALL** PCSK9 inhibitors - the member's specific contraindication must be provided

4. **ANY** of the following ("a", "b", "c", or "d"):

a. Member has been adherent to high-intensity statin therapy (i.e., rosuvastatin greater than or equal to 20 mg daily, atorvastatin greater than or equal to 40 mg daily) for greater than or equal to 8 continuous weeks, and **ANY** of the following ("i", "ii", or "iii"):

i. Member's LDL-C level after this statin therapy remains greater than or equal to 70 mg/dL

ii. Member has not achieved a 50% reduction in LDL-C after this statin therapy

iii. If the member has ASCVD at very high risk, **EITHER** of the following:

1. The member's LDL-C level after this statin therapy remains greater than or equal to 55 mg/dL

2. The member's non-HDL-C level after this statin therapy remains greater than or equal to 85 mg/dL

b. Member has been determined to be statin intolerant by meeting **ANY** of the following criteria ("i", "ii", or "iii"):

i. Member experienced statin-related rhabdomyolysis

ii. Member experienced skeletal-related muscle symptoms [e.g., myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness)], and **BOTH** of the following:

- The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products)
- When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin)

iii. Member experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products)

c. Member has a hypersensitivity to **BOTH** atorvastatin and rosuvastatin

d. Member has an FDA-labeled contraindication to **BOTH** atorvastatin and rosuvastatin - the member's specific contraindication must be provided

5. Member will **NOT** be using the requested agent in combination with a PCSK9 inhibitor [e.g., Praluent (alirocumab), Repatha (evolocumab)] for the requested indication
6. Prescriber is a specialist in the area of the member's diagnosis (e.g., cardiologist, endocrinologist, physician who focuses on the treatment of cardiovascular risk management, lipid specialist), or the prescriber has consulted with a specialist in the area of the member's diagnosis
7. The requested dosage of inclisiran does not exceed 284 mg administered as a single subcutaneous injection initially (Day 0), again at 3 months, and then every 6 months; **OR** does not exceed the FDA-labeled dosing for the requested indication

Approval duration: 12 months

Continuation of inclisiran (Leqvio) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. An authorization or reauthorization for inclisiran has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of HeFH, ASCVD, primary hyperlipidemia, or 10-year ASCVD risk ≥20%; or another FDA-approved indication (if another health plan, documentation of a health plan-paid claim for inclisiran within the past year must be submitted), **OR** the member has previously met **ALL** indication-specific initiation criteria
2. Member has had clinical benefit with inclisiran
3. **ANY** of the following ("a", "b", or "c"):
   a. Member is on a maximally tolerated statin containing lipid-lowering regimen (i.e., rosuvastatin in combination with ezetimibe **OR** atorvastatin in combination with ezetimibe)
   b. Member has an intolerance or hypersensitivity to a statin containing lipid-lowering regimen (i.e., rosuvastatin in combination with ezetimibe **AND** atorvastatin in combination with ezetimibe) - the member's specific intolerance or hypersensitivity must be provided
   c. Member has an FDA-labeled contraindication to **ALL** statin containing lipid-lowering regimens - the member's specific contraindication must be provided
4. Member will **NOT** be using the requested agent in combination with a PCSK9 inhibitor [e.g., Praluent (alirocumab), Repatha (evolocumab)] for the requested indication

5. Prescriber is a specialist in the area of the member's diagnosis (e.g., cardiologist, endocrinologist, physician who focuses on the treatment of cardiovascular risk management, lipid specialist), or the prescriber has consulted with a specialist in the area of the member's diagnosis
6. The requested dosage of inclisiran does not exceed 284 mg administered as a single subcutaneous injection initially (Day 0), again at 3 months, and then every 6 months; **OR** does not exceed the FDA-labeled dosing for the requested indication

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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).
- The recommended dose, in combination with statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months. If a planned dose is missed by less than 3 months, administer inclisiran and maintain dosing according to the patient's original schedule. If a planned dose is missed by more than 3 months, restart with a new dosing schedule - administer inclisiran initially, again at 3 months, and then every 6 months. Assess LDL-C when clinically indicated. The LDL-lowering effect of inclisiran may be measured as early as 30 days after initiation and anytime thereafter without regard to timing of the dose.
- Inclisiran should be administered by a healthcare professional. Inject subcutaneously into the abdomen, upper arm, or thigh. Do not inject in areas of active skin disease or injury, such as sunburns, skin rashes, inflammation, or skin infections.

Dose Adjustments

- Hepatic impairment - No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Inclisiran has not been studied in patients with severe hepatic impairment.
- Renal impairment - No dosage adjustment is necessary in patients with mild, moderate, or severe renal impairment. Inclisiran has not been studied in patients with end-stage renal disease.
- Adverse events - No dosage adjustments are recommended for adverse events.

Drug Availability

- Carton containing one single-dose prefilled syringe of inclisiran 284 mg/1.5 mL (189 mg/mL)
- Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with allowable excursions between 15°C and 30°C (59°F and 86°F).

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Patients with a prior serious hypersensitivity reaction to inclisiran or any of the excipients in Leqvio. Serious hypersensitivity reactions have included angioedema.

Precautions/Warnings

- **Adverse Reactions**: Adverse reactions led to discontinuation of treatment in 2.5% of patients treated with inclisiran and 1.9% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with inclisiran were injection site reactions (0.2% versus 0% for inclisiran and placebo, respectively).
- **Immunogenicity**: As with all oligonucleotides, there is potential for immunogenicity. In the placebo-controlled clinical trials, 1830 patients had samples tested for anti-drug antibodies. Confirmed positivity was detected in 33 (2%) patients prior to dosing and in 90 (5%) patients during the 18 months of treatment with inclisiran. Approximately 31 (2%) inclisiran-treated patients with a negative sample at baseline had a persistent anti-drug antibody response, defined as two confirmed positive samples separated by at least 16 weeks or a single confirmed positive final sample. There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacodynamic profile, clinical response, or safety of inclisiran, but the long-term consequences of continuing inclisiran treatment in the presence of anti-drug binding antibodies are unknown.
- **Pregnancy:** There are no available data on the use of inclisiran in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Discontinue \when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

BILLING/CODING INFORMATION:

HCPCS Coding

J1306	Injection, inclisiran, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia
E78.2	Mixed hyperlipidemia
E78.4	Other hyperlipidemia
E78.49	Other hyperlipidemia, familial combined hyperlipidemia
E78.5	Hyperlipidemia, unspecified
E78.9	Disorder of lipoprotein metabolism, unspecified
I20.2	Refractory angina pectoris
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21.01 – I21.A9	Acute myocardial infarction
I22.0 – I22.9	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction

I23.7	Postinfarction angina
I24.0	Acute coronary thrombosis not resulting in myocardial infarction
I24.8	Other forms of acute ischemic heart disease
I25.10 - I25.9	Chronic ischemic heart disease
I63.00 – I63.9	Cerebral infarction
I65.01 – I65.9	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66.01 – I66.9	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67.2	Cerebral atherosclerosis
I67.81	Acute cerebrovascular insufficiency
I67.82	Cerebral ischemia
I67.89	Other cerebrovascular disease
I67.9	Cerebrovascular disease, unspecified
I68.8	Other cerebrovascular disorders in diseases classified elsewhere
I70.0 – I70.92	Atherosclerosis
I73.89	Other specified peripheral vascular diseases
I73.9	Peripheral vascular disease, unspecified
I74.01 – I74.9	Arterial embolism and thrombosis
I75.011 – I75.89	Atheroembolism
Z95.1	Presence of aortocoronary bypass graft
Z95.5	Presence of coronary angioplasty implant and graft
Z95.820	Peripheral vascular angioplasty status with implants and grafts
Z98.61	Coronary angioplasty status
Z98.62	Peripheral vascular angioplasty status

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

None

RELATED GUIDELINES:

Apheresis, Plasmapheresis and Plasma Exchange, 02-33000-17

Evinacumab-dgnb (Evkeeza), 09-J3000-99

Lomitapide (Juxtapid) Oral, 09-J1000-92

Mipomersen Sodium (Kynamro) Injection, 09-J1000-93

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/11/24.

GUIDELINE UPDATE INFORMATION:

03/15/22	New Medical Coverage Guideline.
07/01/22	Revision: Added HCPCS code J1306 and deleted code J3490.
10/01/22	Revision: ICD-10 code updates.
10/15/23	Review and revision to guidelines consisting of updates to the description, position statement, dosage/administration, precautions, and references. The position statement now includes the additional indications of primary hyperlipidemia in certain members and members with greater than or equal to 20% 10-year ASCVD risk. Added a new LDL-C threshold of greater than or equal to 55 mg/dL for members with ASCVD and at very high risk.
10/15/24	Review and revision to guidelines consisting of updates to the description, position statement, precautions, and references.